Pesticides
(version updated January 3, 2011)

Table of Contents

1.1 Introduction

Many active ingredients in pesticides operate through well-established modes of action. Some pesticides, insecticides in particular, act through neurotransmitter or ion channel systems that are also involved in regulating pancreatic and adrenal function (Table 1). This raises the possibility that these compounds might be able to affect glucose homeostasis, at least at dose levels where they are effective pesticides (Franklin and Wollheim 2004; Satin and Kinard 1998b). This question has been most studied from a toxicological perspective for the organophosphate (OP) pesticides, amitraz, and Vacor although other pesticides belong to the same general chemical class as agents either used to manage diabetes or being researched for their value as therapeutic agents, e.g., sulfonylurea herbicides and imidazole fungicides. Much less research has focused on whether pesticides have activities that might affect adiposity or other risk

Table 1. Biological activities of certain pesticide classes

Chemical Class	Biochemical or Cellular Target	Mechanism of Action
organophosphate and carbamate	acetylcholine	cholinesterase inhibition
neo-nicotinoids	acetylcholine	nicotinic acetylcholine receptors (nAChRs) agonist
pyrethroids	sodium (Na^+) channels	prolonged opening of Na^+ channels
organochlorines	γ-aminobutyric acid (GABA)	GABA antagonist
amidine/formamidine	catecholamines	α2-adrenoreceptors agonist
rotenone	mitochondria	inhibit mitochondrial electron transport chain (complex I)

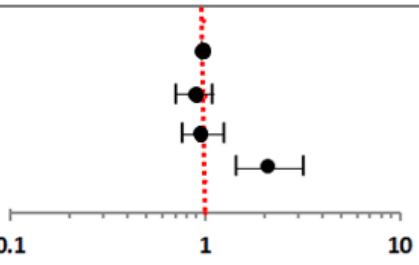
factors for metabolic syndrome. This chapter summarizes findings for pesticides other than the persistent organochlorines.[1] Those compounds are discussed in the persistent organic pollutant (POPs chapter).

1.2 Epidemiology studies

With the exception of studies of persistent organochlorine pesticides, there is very little epidemiological data on other pesticides and health conditions related to diabetes, metabolic syndrome, or adiposity. One study by Saldana et al. (2007) looked at the association between pesticide use during the first trimester of the most recent pregnancy and self-reported gestational diabetes mellitus (GDM) in 11,273 women participating in the Agricultural Health Study (AHS). The AHS is large study of licensed pesticide applicators and their families in Iowa and North Carolina (http://aghealth.nci.nih.gov/). Women who reported agricultural exposure, defined as mixing or applying pesticides to crops or repairing pesticide application equipment, were significantly more likely to report GDM (odds ratio 2.2, 95%CI 1.5-3.3) (Figure 1). Based on additional analyses of the women who reported agricultural exposure during pregnancy, "ever" use of four herbicides (2,4,5-TP, 2,4,5-T, atrazine, and butylate) and three insecticides (diazinon, phorate, and carbofuran) were significantly associated with increased risk of GDM (Figure 2). The three insecticides belong to pesticide classes that act via cholinesterase inhibition (OPs or carbamates).

Figure 1. Adjusted ORs for self-reported gestation diabetes mellitus (GDM) and pesticide exposure category among wives of farmers in the Agricultural Health Study (1993-1997)

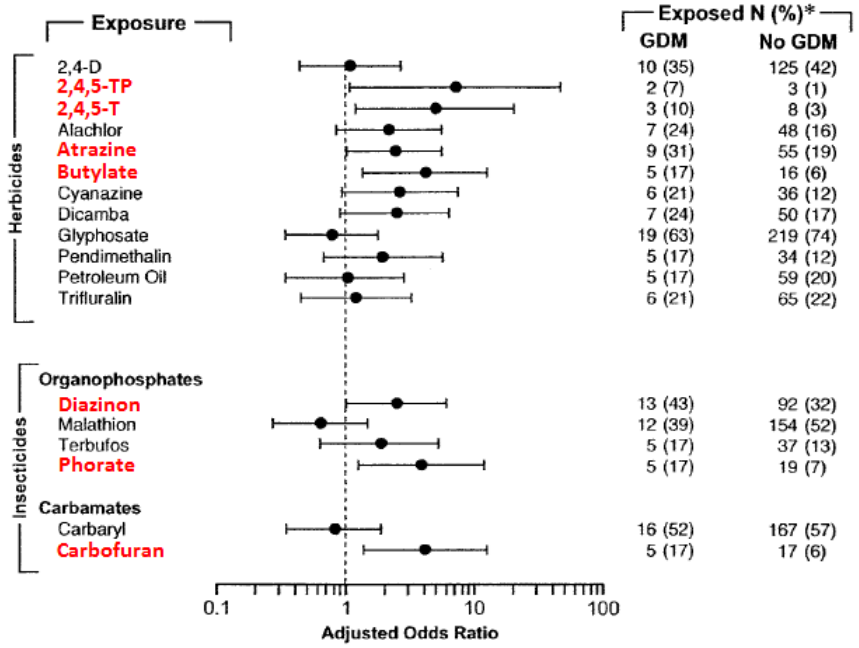
Pesticide Exposure Category	Number (%) GDM N = 506	Number (%) No GDM N = 10,767	Adjusted Odds Ratio (95%CI)
None	233 (46)	4918 (46)	1
Indirect	157 (31)	3724 (35)	0.9 (0.7-1.1)
Residential	84 (17)	1820 (17)	1.0 (0.8-1.3)
Agricultural	32 (6)	305 (3)	2.2 (1.5-3.3)



Models adjusted for BMI at enrollment, mother's age at pregnancy, parity, race, and state. Indirect exposures include planting, pruning, weeding, picking, or harvesting. Residential exposures include applying pesticides to garden or inside house. Agricultural exposures include mixing or applying pesticides to crops or repairing pesticide application equipment. From Saldana et al. (2007)

[1] *p,p'*-DDT/*p,p'*-DDE/*o,p'*-DDE, trans-nonachlor, oxychlordane, mirex, hepatachlor epoxide, β hexachlorocyclohexane (β-HCH), lindane or γ-HCH, hexachlorobenzene (HCB)

Figure 2. Pesticide-specific ORs for GDM among wives of farmers in the AHS reporting agricultural exposure during pregnancy



*Pesticides in red have elevated adjusted ORs that are statistically significant.
Individual models adjusted for BMI at enrollment with categories of <18.5 and 18.5–24.9 kg/m^2 combined, mother's age at pregnancy, parity, race, state, and commonly used pesticides by women. The numbers included in pesticide-specific analysis differ due to missing data. Among women who reported agricultural exposure during pregnancy, the number of women with GDM ranges from 29 to 32 and the number of women without GDM ranges from 281 to 297. Statistically significant associations are highlighted in red.
From Saldana et al. (2007)

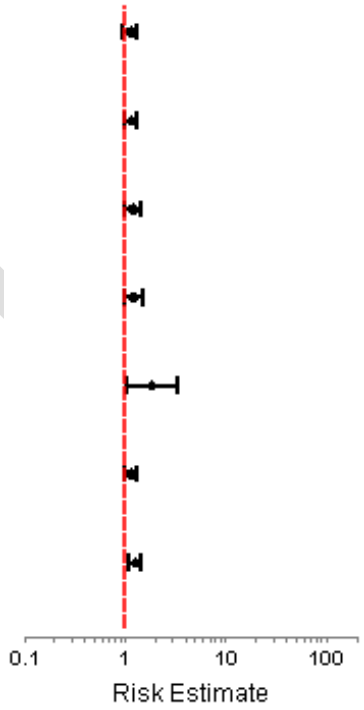
Montgomery et al. (2008) also made use of the AHS cohort to look at incident diabetes in 31,787 pesticide applicators (97.4% men) who did not have diabetes at baseline (1993-1997). At 5-year follow-up during 1999-2003, approximately 3.7%, or 1,176 of the pesticide applicators self-reported being diagnosed with diabetes by a doctor. Exposure to ~50 insecticides and herbicides[2] was considered in the study with pesticide exposure analyzed based on "ever use" as well as cumulative days of use (never, 0.01-10, 10.01-100, or >100 days) for a subset. The odds of diabetes incidence were considered by the author's increased with both ever use and cumulative days of use for 7 specific pesticides: aldrin, chlordane, heptachlor, dichlorvos, trichlorfon, alachlor, and cyanazine. The magnitudes of the associations were stronger in applicators with higher body mass index. The adjusted ORs for under or

[2] **7 organochlorines:** aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphene; **10 organophosphates**: chlorpyrifos, coumaphos, diazinon, dichlrovos, fonofos, malathion, parathion, phorate, terbufos, trichlorfon; **3 carbamates:** aldicarb, carbaryl, carbofuran; **1 pyrethroid:** permethrin (crop or animal); **18 herbicides:** 2,4,5-T, 2,4,5-TP, 2,4-D, alachor, atrazine, butylate, chlorimuron-ethyl, cyanazine, dicambra, EPTC, glyphosate, metolachlor, metribuzin, paraquat, pendimethalin, petroleum oil, trifluralin; **6 fungicides**: benomyl, captan, chlorothalonil, maneb, metalaxyl, ziram; and **4 fumigants**: aluminum phosphide, carbon tetrachloride, ethylene dibromide, methyl bromide

normal weight (BMI<25) versus obese (BMI≥30) were: aldrin (0.53 vs1.31), chlordane (1.02 vs 1.19), hepatochlor (0.48 vs 1.42), dichlorvos (1.03 vs 1.30), alachlor (0.82 vs 1.24), cyanazine (0.62 vs 1.27).

Table 2. Pesticides for which the odds of diabetes incidence increased with both ever use or cumulative days of exposure in licensed pesticide applicators participating in the Agricultural Health Study

Pesticide	N in analysis	Cumulative days of exposure*	adjusted OR (95%CI)
aldrin (organochlorine)	n = 5,678 (261 diabetics/5,417 non-diabetics) 70 exposed cases (27%)	p-trend = 0.08	
chlordane (organochlorine)	n = 7,737 (372 diabetics/7,365 non-diabetics) 141 exposed cases (38%)	p-trend = 0.05	
hepatochlor (organochlorine)	n = 4,778 (209 diabetics/4,569 non-diabetics) 46 exposed cases (22%)	p-trend = 0.02	
dichlorvos (organophosphate)	n = 3,215 (110 diabetics/3,105 non-diabetics) 12 exposed cases (11%)	p-trend = 0.15**	
trichlorfon (organophosphate)	n = 182 (13 diabetics/169 non-diabetics) 1 exposed case (1%)	p-trend = 0.02	
alachlor (chloroacetanilide)	n = 15,779 (585 diabetics/15,194 non-diabetics) 339 exposed case (58%)	p-trend = 0.001	
cyanazine (chlorotriazine)	n = 12,442 (408 diabetics/12,034 non-diabetics 163 exposed case (40%)	p-trend = 0.004	



Study Design: 31,787 licensed private pesticide applicators (97.4% male) that did not have diabetes at baseline in the Agricultural Health Study. Follow-up interviews were conducted 5 years later (1999-2003) and diabetes was assessed by self-report of doctor's diagnosis.

*p-trend for the following categories of cumulative days of use: "never," "0.01-10," "10.01-100," and ">100"; p-trend of < 0.10 was considered indicative of a dose-response.

** Although the p-trend is not statistically significant at p<0.10 for dichlorvos, the authors considered it to have a moderate dose-response trend because the ORs within each specific cumulative exposure category increased with more days of use: 0.01-10 days = 1.15 (95%CI 0.78-1.67); 10.01-100 = 1.19 (95%CI 0.82-1.72); and >100 days = 1.26 (95%CI 0.91-1.73)

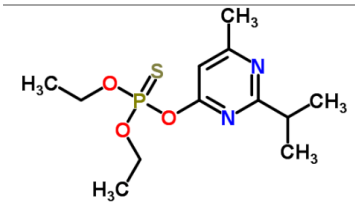
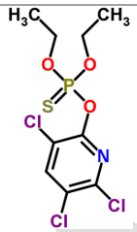
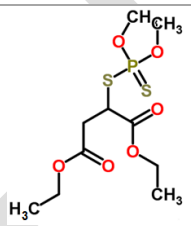
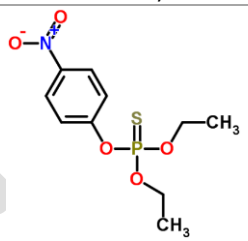
From Montgomery et al. (2008)

1.3 Organophosphate insecticides

The mechanism of action for the systemic toxicity of OP insecticides is inhibition of acetylcholinesterase, more commonly referred to as cholinesterase. Inhibition of this enzyme has the effect of increasing levels of the neurotransmitter acetylcholine (ACh), a major neurotransmitter in both the peripheral parasympathetic and central nervous systems. At lower levels of exposure, however, these agents exert multiple actions, including effects on a variety of enzymes and signaling pathways that are relevant to metabolism. Acetylcholine has a physiological role in regulating levels of glucose and insulin by promoting pancreatic insulin secretion (Gautam *et al.* 2010), increasing

peripheral and liver glucose uptake, and stimulating the adrenal medulla to secrete norepinephrine and epinephrine which results in increased blood glucose and metabolic activity (Edwards and Jones 1993; Garcia *et al.* 1988; Ilcol *et al.* 2002; Laine *et al.* 1996; Pilo and Mehan 1987; Satin and Kinard 1998a; Umegaki *et al.* 2000; Verchere *et al.* 1991). In addition to cholinesterase inhibition, data from EPA's high throughput screening program (ToxCast™) conducted through the Tox21 initiative[3], indicates that certain OPs or their metabolites can interact with a number of receptor systems relevant to energy regulation, including PPARγ (see hyperlinks to ToxCast™data in Figure 3).

Figure 3

Diazinon	Chlorpyrifos	Malathion	Parathion
333-41-5	2921-88-2	121-75-5	56-38-2
$C_{12}H_{21}N_2O_3PS$ (MW 304.35)	$C_9H_{11}Cl_3NO_3PS$ (MW 350.59)	$C_{10}H_{19}O_6PS_2$ (MW 330.36)	$C_{10}H_{14}NO_5PS$ (MW 291.26)
			
Hyperlinks to ToxCast™data for the parent OP and/or metabolites: These data are also in Appendix B, sorted by lowest to highest AC_{50}, with the official full name of the gene			
diazinon & diazoxon	chlorpyrifos oxon & chlorpyrifos methyl	malathion	parathion & parathion methyl

There is a relatively large literature reporting effects of intoxication with OP insecticides on glucose in laboratory animals, generally in the direction of hyperglycemia at high dose levels [Appendix Table A; see also review by Rahimi and Adbollahi (2007) and Karami-Mohajeri (2010)]. Recently, the literature has shifted towards studies designed to understand the consequences of developmental exposure to relatively low doses of OPs and long-term health effects related to metabolic dysfunction, diabetes, and obesity later in life (Adigun *et al.* 2010a; Adigun *et al.* 2010b, c; Icenogle *et al.* 2004; Lassiter *et al.* 2010; Lassiter *et al.* 2008; Levin *et al.* 2002; Roegge *et al.* 2008; Slotkin *et al.* 2005; Slotkin *et al.* 2009a) [reviewed in Slotkin (2010)]. Several of these more recent studies also looked at how metabolic parameters can be altered in animals treated with OPs during development and subsequently placed on a high fat diet in adulthood (Adigun *et al.* 2010a; Lassiter *et al.* 2010; Slotkin *et al.* 2009a). The general findings are that early-life exposure to otherwise subtoxic levels of OPs reprograms metabolism so as to produce subsequently-emerging pre-diabetes, abnormalities of lipid metabolism, and promotion of obesity in response to increased dietary fat.

[3] Tox21 is a collaborative program between the EPA, NIEHS/NTP, NIH/NCGC, and FDA designed to research, develop, validate and translate innovative chemical testing methods that characterize toxicity pathways. Information on ToxCast and Tox21 is available at http://epa.gov/ncct/Tox21/ as well as overviews by Judson et al. (2010), Reif et al. (Reif *et al.* 2010), and Shukla et al. (2010).

Glucose homeostasis

A literature dating back to the 1970s shows that organophosphate pesticides (OPs) can cause hyperglycemia in experimental animals, typically under conditions of acute treatment with high dose levels of malathion or diazinonin rats, fish, eels and crabs (Agarwal and Matin 1981; Bhagyalakshmi *et al.* 1982; Bhagyalakshmi *et al.* 1983; Koundinya and Ramamurthi 1979; Matin and Husain 1987; Matin and Siddiqui 1982; Ramu and Drexler 1973; Reena *et al.* 1989; Seifert 2001; Srivastava and Singh 1981)[see also review by Rahimi and Adbollahi (2007) and Appendix Table A]. These findings are consistent with reports of hyperglycemia in cases of human poisoning with OPs (Agency for Toxic Substances and Disease Registry (ATSDR) 1997; Sungur and Guven 2001). One case series report by Ramu et al. (1973) described effects on glucose in relation to cholinesterase levels in 9 Israeli children who experienced OP poisoning after using a hair wash containing malathion to eradicate lice. Hyperglycemia, indicated by blood glucose levels of 344 to 756 mg/100 ml, was observed in all 4 children considered to have severe poisoning (serum cholinesterase levels were not detectable). For comparison purposes, the children characterized as asymptomatic had blood glucose levels in the normal range of 88 to 102 mg/100 ml and serum cholinesterase levels of 3.1 to 4.0 units/ml.

Many of the animal studies reporting hyperglycemia treated fasted rats or mice with a single oral or ip injection dose level considered high for the specific OP tested: malathion at 200 mg/kg to 2,500 mg/kg (Agarwal and Matin 1981; Lasram *et al.* 2009; Matin and Husain 1987; Matin and Siddiqui 1982; Ramu and Drexler 1973; Rodrigues La *et al.* 1986), acephate at 140 mg/kg (Joshi and Rajini 2009), and diazinon at 20 mg/kg to 150 mg/kg (Husain and Ansari 1988; Matin *et al.* 1990a; Matin *et al.* 1989; Matin *et al.* 1990b; Seifert 2001). The effects on glucose from acute high dose treatments in adult animals tend to be transient and normalize within several days of the exposure (Joshi and Rajini 2009; Lasram *et al.* 2009; Seifert 2001). The hyperglycemic response is often accompanied by changes in lipid levels, glycogen content of the liver and/or brain, and activity of liver enzymes associated with gluconeogenesis, glycolysis, or glycogenesis (Abdollahi *et al.* 2004; Afshar *et al.* 2008; Agarwal and Matin 1981; Gowda *et al.* 1983; Husain and Ansari 1988; Lasram *et al.* 2009; Matin *et al.* 1989; Sastry and Siddiqui 1982). These latter findings are more inconsistent in terms of direction of effect and it's difficult to try and reconcile the literature because of variation in the endpoints assessed and other features of experimental design such as specific OP tested (i.e., malathion, diazinon, fenitrothion, acephate), dose level used, sex tested, and route of administration (oral or injection). The overall pattern of response has been suggested as indicating increased hepatic glucose output via gluconeogenesis (Joshi and Rajini 2009). The conclusions from a review of mechanisms of OP-induced hyperglycemia by Rahimi and Abdollahi (2007) were that most studies indicated that OPs can induce metabolic pathways in brain, skeletal muscles, and liver in favor of increased glucose production.

One of the more detailed assessments of OP-induced hyperglycemia was a study with diazinon by Seifert et al. (2001). This study characterized blood glucose in young adult Swiss albino mice that were treated with a single ip injection of diazinon under different experimental designs, including a dose response assessment, a time course assessment of hyperglycemic response, comparison of response in feed restricted and ad libitum fed animals, and impact of time of day. In the dose response study, non-fasted blood glucose measured at 1.5 hours after treatment was significantly elevated at 75, 100, 150,

or 250 mg/kg diazinon, but not at the lowest tested dose level of 20 mg/kg (the 150 mg/kg dose was selected for other experiments). With respect to time course, an increase in blood glucose was observed at 3 hours after treatment with 150 mg/kg diazinon (~3.24-fold times higher than historical control values), persisted through 6 days (~1.25-fold higher at 150 hours), and declined to control levels by 200 hours. Whole brain levels of cholinesterase during the period of hyperglycemia decreased from ~80% to ~60% of control levels.

The findings are somewhat more inconsistent for effects on glucose in subchronic studies that used lower dose levels than in the acute studies (Appendix Table A). Increased fasting plasma glucose was reported in adult rats treated with malathion (Abdollahi *et al.* 2004; Panahi *et al.* 2006; Pournourmohammadi *et al.* 2005), fenitrothion (Afshar *et al.* 2008), and acephate (Deotare and Chakrabarti 1981). Impaired glucose tolerance was found in adult male CFT-Wistar rats orally treated with 20 or 40 mg/kg dimethoate for 30 days (Kamath and Rajini 2007). Hagar et al. (2002) reported increased serum glucose and decreased insulin in adult male Wistar rats treated with 21 mg/kg dimethoate by oral gavage for 2 months. These effects persisted in animals given a 1-month recovery period and were linked to histological and biochemical changes in the pancreas (discussed below).

In contrast, no effects on fasting blood glucose were reported by Sadeghi-Hashjin (2008) in a study were mice were treated with 0, 0.1, 1% azynphos methyl or malathion by 10-second tail dip once a day for a week, although there was some suggestion that the OPs might have suppressed the normal post-prandial increase in blood glucose observed after feeding. No effect on blood glucose was reported by Gowda et al. (1983) in adult male Wistar rats treated with 46 mg/kg malathion for 15 days was reported although increases in liver glycogen were found. Rezg et al. (2007) did not find hyperglycemia in adult male Wistar rats treated by gavage with 100 mg/kg-da malathion for 32 days and suggested the hyperglycemic responses can be temporary and corrected overtime by stimulation of glycogenesis increases hepatic glycogen deposition and the return of glucose to control levels.

Long-term effects on glucose and insulin have been reported in several studies where neonatal rats were treated with OPs on PND1-4 by sc injection (Table 6). As noted above, the dose levels selected in these studies were designed to be non-symptomatic, straddling the threshold for barely-detectable cholinesterase inhibition and were matched across the different OPs tested to be bioequivalent for that endpoint. In adulthood, these animals all developed metabolic profiles resembling pre-diabetes, although the exact patterns differed among the various OPs. All the OPs up-regulated the hepatic response to gluconeogenic signals (beta-adrenergic or glucagon input), as monitored by the effects of receptor agonists on adenylyl cyclase, the signaling pathway that transduces neuronal and hormonal signals into metabolic chanages. For chlorpyrifos, the animals maintained normal serum glucose levels in the face of this abnormality by hypersecreting insulin; accordingly there were corresponding abnormalities in lipid metabolism and other insulin-driven metabolic parameters. When animals were fasted to eliminate hepatic gluconeogenesis, the hyperinsulinemia disappeared, demonstrating that the syndrome indeed was driven by the targeting of hepatic function. After early-life parathion exposure, the animals became frankly hyperglycemic and similarly showed changes in lipid metabolism and circulating adipokines similar to effects seen in pre-diabetes. Regardless of which OP was given (chlorpyrifos, diazinon, parathion), the animals all displayed abnormal weight gain that was

exacerbated by a high-fat diet; the diet also worsened the pre-diabetic metabolic profiles (Lassiter *et al.* 2010; Lassiter *et al.* 2008; Slotkin *et al.* 2005).

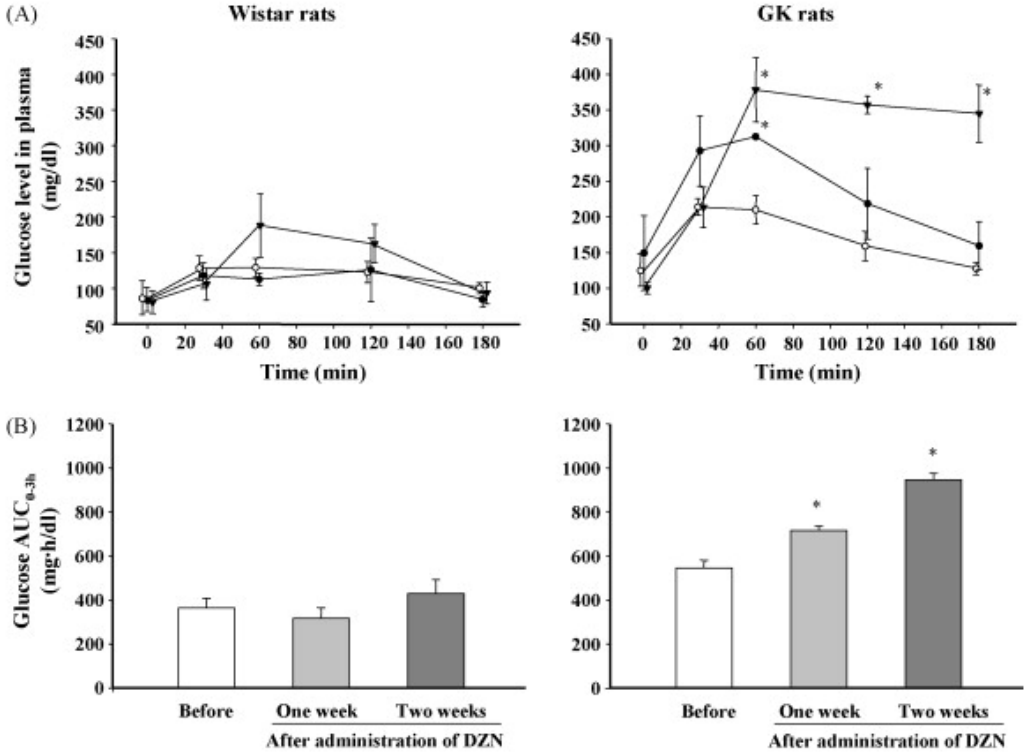
Another study in adults looked at the effect of diazinon on glucose tolerance in Goto-Kakizaki (GK) rats, a model for mild type 2 diabetes developed by selective inbreeding of Wistar rats with the highest blood glucose levels during an oral glucose tolerance test (Ueyama *et al.* 2008). Male Wistar and the GK rats received a single ip injection at 0 or 6.5 mg/kg bw diazinon. Three-hour OGTTs were conducted pre-treatment and at 1 and 2 weeks post treatment. No effects of diazinon were observed in the non-diabetic Wistar rats but statistically significant increases in plasma glucose area under the curve (AUC) were seen in the GK rats even 2 weeks after treatment (Figure 4). It is not clear why glucose tolerance was impaired in the GK rats. Insulin levels were unaffected by diazinon[4] and there were no indications of pancreatic histopathology (i.e., massive necrotic areas, infiltration of inflammatory cells) or differences in the structure and number of islet immunoreactive insulin-positive cells. Diazinon did not affect GLUT4 expression in adipose tissues in either Wistar or GK rats. The impaired glucose tolerance also did not appear to be due to differences in the Wistar and GK rats with respect to the extent of cholinesterase inhibition or activity/expression of a number of hepatic cytochrome 450s involved in diazinon metabolism.

Pancreatic effects

Acetylcholine acts to promote pancreatic insulin release (Azua *et al.* 2010; Garcia *et al.* 1988; Henquin *et al.* 1988; Nakano *et al.* 2002; Satin and Kinard 1998a; Verchere *et al.* 1991).The effects of acetylcholine in the pancreas are thought to be mediated primarily via muscarinic receptors (Gautam *et al.* 2010), although nicotinic receptors may also be involved (Ilcol *et al.* 2008; Ilcol *et al.* 2002) [four assays for muscarinic receptors are included in Phase 1 of Toxcast™, CHRM1, CHRM2, CHRM3, and CHRM4]. In humans, acute pancreatitis has been reported in cases of poisoning with several OPs, including mevinphos (Hsiao *et al.* 1996), parathion (Lankisch *et al.* 1990; Weizman and Sofer 1992), malathion (Dagli and Shaikh 1983), diazinon (Weizman and Sofer 1992), coumaphos (Moore and James 1981), difonate (Dressel *et al.* 1979), and dimethoate (Marsh *et al.* 1988).

[4] DZN had no effect on plasma insulin levels in either Wistar or GK rats before and 90 min after glucose administration, Wistar (1.3±0.3 and 1.2±0.5 ng/ml, respectively) and GK rats (0.7±0.2 and 0.9±0.1 ng/ml, respectively).

Figure 4. Impaired glucose tolerance in mildly diabetic GK rats treated with diazinon



Plasma concentration–time curves (A) and area under curves (AUC) (B) of glucose in Wistar and GK rats before (open circle), 1 week (closed circle) and 2 weeks (closed triangle) after ip injection of diazinon (6.5 mg/kg). Rats received oral administration of glucose (2 g/kg). Each plot represents the mean ± S.E.M. (n = 3–4). *Significantly different from DZN-untreated rats ($P < 0.05$).
Reprinted from Ueyama et al. (2008) with permission from publisher.

Pancreatic effects have also been reported in animals treated with OPs (Arsenault and Gibson 1974; Arsenault *et al.* 1975; Hagar *et al.* 2002; Kamath and Rajini 2007; Laley and Gibson 1977). In some cases, apparently inconsistent effects on blood glucose may be explained by understanding what is happening at the level of the pancreas. One research group evaluated the histogenesis of islets of Langerhans and blood glucose in White Leghorn chick embryos injected on incubation day 5 with 0.1 mg of 2% malathion (Arsenault and Gibson 1974; Arsenault *et al.* 1975; Laley and Gibson 1977)[5]. The percent of pancreatic tissue characterized as β tissue was increased by the treatment and the embryos were hypoglycemic (Table 3) which the authors attributed to increased insulin secretion from the pancreas by virtue of the increase in β-cell mass.

[5] This research question was of interest based on apparent similarity in a birth defect, micromelia (abnormal shortness of limbs), associated with both insulin and malathion treatment.

Table 3. Histogenesis of the islets of Langerhans and blood glucose during incubation in White Leghorn chick embryos treated with a single injection of 0.1 mg of 2% malathion in corn oil on incubation day 5

	untreated embryos			malathion-treated embryos[2]		
days of incubation	α tissue (%)[1]	β tissue (%)[1]	blood glucose[2]	α tissue (%)[1]	β tissue (%)[1]	blood glucose[2]
11	4.57	4.52	146.07	3.25	7.82	110.16*
13	6.90	5.50	143.75	14.88*	15.68*	107.70*
15	10.88	8.36	150.31	18.31*	17.73*	126.75*
17	17.01	11.36	152.75	16.41	21.72*	111.50*
19	15.78	12.52	166.66	18.25	15.10	137.11*

[1]From Arsenault and Gibson (Arsenault and Gibson 1974), n = 4-6 per group, data expressed as percentage of pancreatic tissue

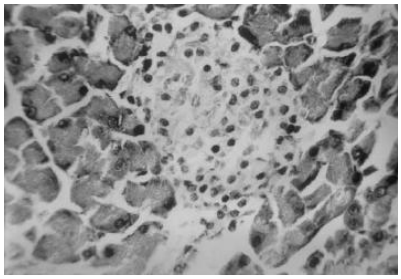
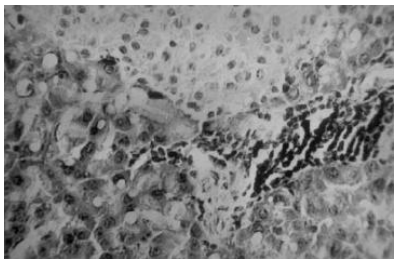
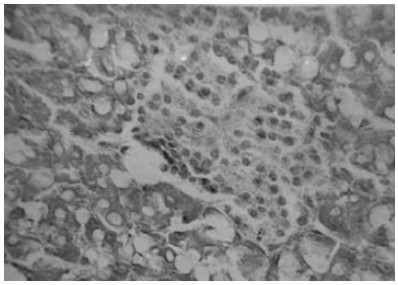
[2]From Arsenault et al. (1975), n = 8-18 per group

* Statistically significant difference from untreated embryos, $p<0.05$

Another study reported that longer term treatment with dimethoate to adult Wistar rats (21 mg/kg-d for 2 months) caused patchy degenerative changes of variable severity in islet cells (Hagar *et al.* 2002). These effects persisted in a recovery group of rats evaluated one month after treatment was stopped. In this case, the histological effects in islet cells were accompanied by decreased insulin levels and increased blood glucose (Table 4). Impaired glucose tolerance and indications of oxidative effects in the pancreas were reported in another dimethoate study where male CFT-Wistar rats were orally treated for 30 days with 0, 20, or 40 mg/kg-d (Kamath and Rajini 2007). Animals in both dimethoate treatment groups showed elevated blood glucose in a 3-hour OGTT conducted at the end of the 30 day treatment period. Pancreatic acetylcholinesterase activity was decreased at these dose levels, although this effect was not statistically significant in the 20 mg/kg-d group where activity was 60% of the control value. Significant effects on lipase and amylase enzymes in serum (increased activity) and pancreas (decreased activities) and increases in pancreatic levels of ROS and TBARS were observed in both treatment groups. Effects on pancreatic activities of antioxidant enzymes were observed in one or both treatment groups (↑superoxide dismutase, ↑catalase, ↓ glutathione peroxidase, ↑glutathione reductase, and ↑glutathione S-transferase).

Panahi et al. (2006) reported stimulatory effects of malathion on enzymes involved in insulin secretion in islet cells isolated from adult male Wistar rats fed 0, 100, 200 or 400 ppm of malathion in the diet for 4 weeks. Blood was collected and analyzed for glucose and insulin levels and isolated pancreatic islets were assayed for glutamate dehydrogenase (GDH) and glucokinase (GK) activity. Islet activity of GDH was increased in all treatment groups and GK activity was increased in the 200 and 400 ppm groups. Blood glucose was also increased in all treatment groups and insulin in the 200 and 400 ppm groups. Another study did not report effects on pancreatic glucokinase activity/mRNA levels or insulin mRNA levels were detected in Wistar rats treated with 1 or 3 days of treatment with 20 mg/kg dimethoate (Romero-Navarro *et al.* 2006).

Table 4. Effects on the pancreas, serum glucose, and insulin in adult male Wistar rats treated with dimethoate

Treatment	serum glucose (mg/dl)	insulin (µU/ml)	H&E stain of pancreas (x400)[1]
control, n=10	90.5	33.4	
21 mg/kg d dimethoate for 2 months (oral gavage), n=20	115.1*	23.6*	
21 mg/kg d dimethoate for 2 months (oral gavage) followed by 1-month recovery, n=20	110.3*	24.2*	

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[1]Effects on the islet cells in the dimethoate treatment groups characterized as showing scattered degenerated cells varied from cloudy swelling with granular cytoplasm to hydropic degeneration with vacuolated cytoplasm.
* Statistically significant difference from untreated embryos, $p<0.05$

Adrenal gland

Acetylcholine-induced catecholamine release from the adrenal medulla is primarily mediated by nicotinic receptors (Gurun *et al.* 2002; Yokotani *et al.* 2002) [two assays for nicotinic receptors are included in Phase 1 of Toxcast™, CHRNA4 and Chrna7]. Increased catecholamine secretion can increase blood glucose levels by stimulating the activity of enzymes involved in hepatic glycogenolysis and gluconeogenesis in favor of glucose release into the blood (Abdollahi *et al.* 2004; Felig and Bergman 1995; Joshi and Rajini 2009; Lasram *et al.* 2009). Several studies conducted between 1973 and 1990 looked at the role of the adrenal gland in mediating diazinon or malathion-mediated hyperglycemic response by comparing response in control animals to rats that had been

adrenalectomized prior to treatment with the pesticide (Matin *et al.* 1990a; Matin *et al.* 1989; Matin *et al.* 1990b; Ramu and Drexler 1973) or by administering pharmacological agents shortly after pesticide treatment (Husain and Ansari 1988; Matin and Siddiqui 1982; Ramu and Drexler 1973) (Table 5). All of these studies used a single dose treatment with assessment of glycemic response within hours of dosing. The doses levels of diazinon or malathion used can be considered high, ranging from 40 mg/kg diazinon by ip injection (one-third the LD_{50}) in Husain et al. (1988) to 2 or 2.5 g/kg by sc injection in Ramu et al. (1973). The hyperglycemic response was essentially abolished in animals that underwent adrenalectomy or were co-administered atropine, a cholinergic blocker. Other treatments with α- or β-adrenergic receptor antagonist attenuated the response such that the degree of hyperglycemia was intermediate between control values and animals only treated with the OP pesticide. The involvement of adrenal hormones is also supported by findings in Joshi et al. (Joshi and Rajini 2009) who reported elevated plasma corticosterone levels along with hyperglycemia in rats treated with a single dose of 140 mg/kg of acephate by oral gavage. An exception to this pattern is a study Gowda et al. (1983) where no effect on blood glucose was observed in rats treated with 46 mg/kg by ip injection for 15 days although occasional decreases in adrenal medulla levels of adrenaline, noradrenaline, and dopamine were noted.

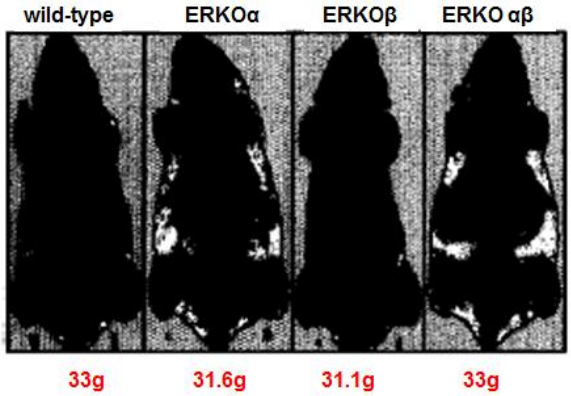
Table 5. Effect of adrenalectomy or pharmacologic interventions in altering diazinon or malathion-induced hyperglycemia.

Pesticide	Effect of OP on blood glucose within hours of treatment	Manipulation and effect	Reference
diazinon single treatment with 40 mg/kg by ip injection to female Wistar rats	↑	tolazoline (α-adrenergic receptor antagonist) attenuated effect on glucose propranolol (β-adrenergic receptor antagonist) attenuated effect on glucose atropine (cholinergic blocker) prevented effect on glucose	Husain and Ansari (1988)
malathion single treatment with 500 mg/kg by ip injection to male albino rats	↑	diacetylmonoxime, DAM (cholinesterase reactivator) attenuated effect on glucose atropine (cholinergic blocker) prevented effect on glucose reserpine no effect on malathion effects on blood glucose	Matin and Siddiqui (1982)
diazinon single treatment with 40 mg/kg by ip injection to female albino rats	↑	adrenalectomy prevented effect on glucose	Matin et al. (1990a; 1989; 1990b)
malathion single treatment with 2 or 2.5 g/kg by sc injection to female rats	↑	pentapyrolidonium attenuated effect on glucose reserpine (depletes catecholamines from peripheral sympathetic nerve ending) no effect on blood glucose adrenalectomy prevented effect on glucose atropine (cholinergic blocker) prevented effect on glucose	Ramu and Drexler (Ramu and Drexler 1973)

Body weight and adiposity and lipids

Most of the studies reporting effects related to OPs as "obesogens" are based on findings in Sprague-Dawley rats treated during PND1-4 with dose levels of chlorpyrifos, diazinon, or parathion that are designed to be non-symptomatic and just at the threshold for barely-detectable cholinesterase inhibition. The dose levels were matched across the chemicals tested based on bioequivalence to achieve equivalent cholinesterase inhibition. The overall picture that emerges for effects of OPs on body weight and growth is complex. The effects are often relatively subtle and not necessarily observed in all studies of the same specific OP or across both sexes within a given study, including in studies that incorporated a secondary challenge with a high fat diet (Table 6). When present, the body weight changes range from less than 5% increase or decrease compared to control values (Adigun *et al.* 2010c; Lassiter *et al.* 2010; Lassiter *et al.* 2008), but with increases of ~1.10 to 1.20-fold reported in studies by Roegge et al. (2008) and Lassiter et al. (2008). None of the studies looked for effects on adiposity or lean body mass. This is a significant limitation of the current literature because it is general accepted that body weight is a relatively crude indicator of internal body fat in rodent models. For example, no changes in body weight were observed by Ohlsson et al.(2000) in estrogen receptorα knockout mice (ERKOα) mice compared to wild-type controls despite having visably greater amounts of adipose tissue (Figure 5).

Figure 5. Lack of relationship between adiposity and body weight in ERKOα mice.



Reprinted from Ohlsson et al. (2000) with permission from publisher.

Changes in leptin levels were difficult to interpret for an overall pattern of response but the study by Lassiter et al. (2008) suggested that developmental treatment with chlorpyrifos may alter the coupling of leptin with body weight. Body weight and leptin were strongly correlated in control rats, both male and female (r=0.93 and 0.87, respectively). Chlorpyrifos exposure weakened the weight–leptin correlation in males (r=0.66) eliminated the statistical significance of the relationship in females (r=0.44). A study by Meggs and Brewer (2007) reported increases in body weight in adult female Long Evans rats treated for several months with a higher dose level of chlorpyrifos than that used by Slotkin et al. (Slotkin *et al.* 2005). The rats were treated with 5 mg/kg-d chlorpyrifos by sc injection for 4 months and body weight increases ranging from 1.05-fold to 1.10-fold were seen at 2 to 4 months. The weight of the peri-nephric fat pad was also increased by 2.5-fold. The authors also looked at the effect of chlorpyrifos on growth, cell number, and fat accumulation in pre-differentiated adipocytes and did not detect an effect at concentrations up to 0.008 µg/ml chlorpyrifos (Meggs and Brewer 2007)

The EPA has compiled an online database of thousands of animal toxicology studies referred to as the Toxicity Reference Database, or ToxRefDB (http://actor.epa.gov/toxrefdb/faces/Home.jsp). The

current version has data for 474 chemicals, mostly pesticide active ingredients. The studies cited are mostly unpublished studies conducted for pesticide registration purposes and are not available in the peer-reviewed literature. ToxRefBD was queried for chemicals that caused increased body weight (or body weight gain), increased glucose, and pancreatic effects and the results presented in Table 9 and Appendix B. Six of the studies identified increased body weight or body weight growth as an outcome from treatment with OPs, including two separate studies for fenthion, one conducted in rats and the other in mice.

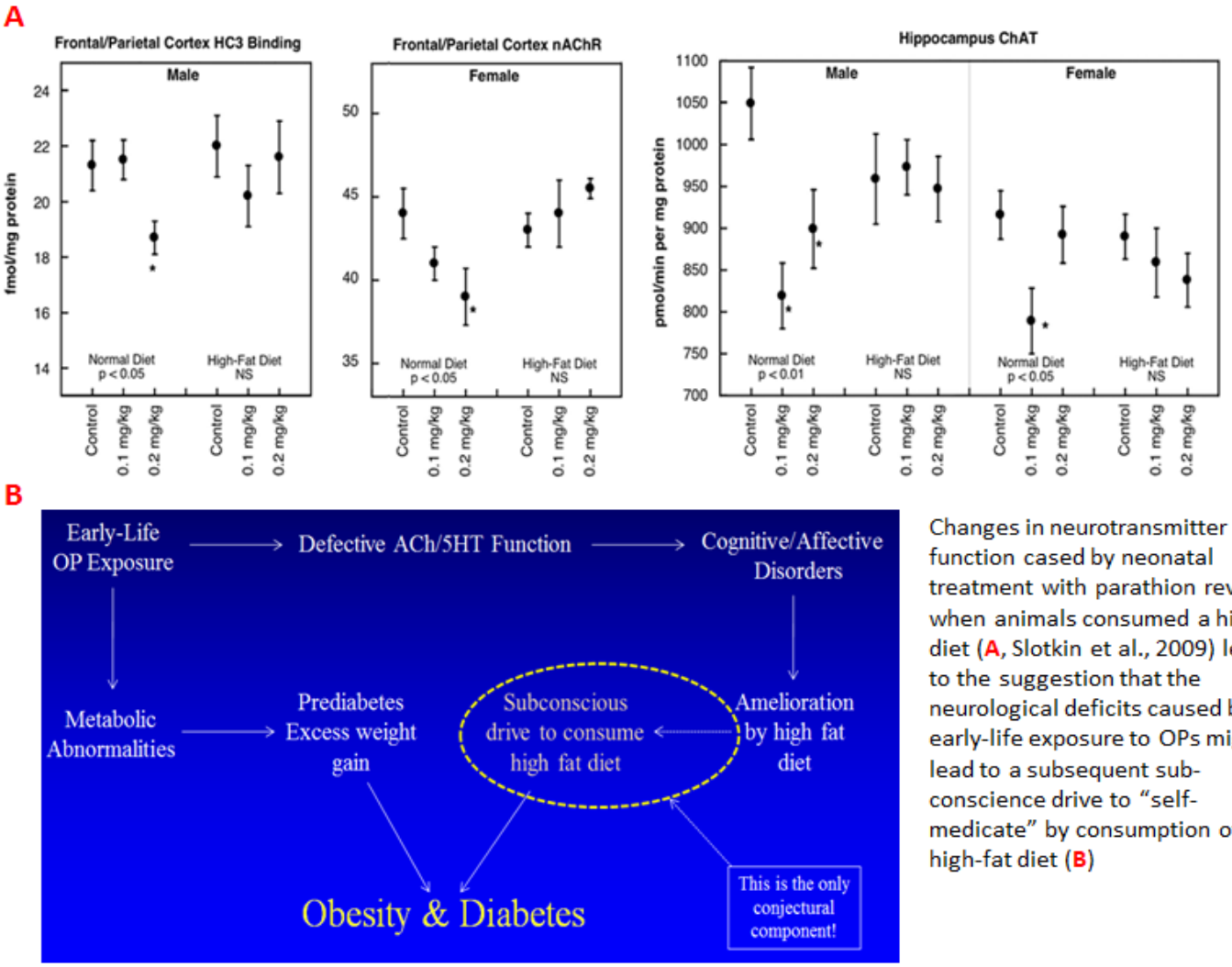
A further complication is the likelihood that the adverse effects of the OPs, and likely many other environmental toxicants, are not monotonically related to the exposure level. Lassiter et al. 2008 (2008) conducted a dose-response study with treatment of 1.0, 2.5, or 4.0 mg/kg of chlorpyrifos from GD7 to PND21 and found that body weight response in males during adulthood was non-monotonic with body weights on PND95-101 that were 104.8, 107.5, or 100.7% of control. This highlights a challenge of using many of the existing toxicology studies to look for "obesity"-like effects, especially those conducted for the purposes of pesticide registration. These studies typically test high dose levels and a common manifestation of high dose toxicity is weight loss. The findings of increased body weight or weight gain presented in Appendix B have not been characterized or discussed to the extent that they need to be. Chemical "obesogens" may have very different effects at low exposures as compared to the high exposures that produce symptoms of acute toxicity.

The current literature lacks measures of (1) energy intake and (2) energy expenditure. Obesity and the metabolic syndrome are consequences of positive energy balance. Positive energy balance occurs as a result of increased energy intake, decreased energy expenditure or both, and the effects of pesticide exposure on these indices are essentially unexplored. The hypothalamus is involved in regulating appetite and other food intake aspects of energy regulation (Berthoud and Morrison 2008; Woods 2009). Another area that probably deserves more attention is inflammation. A recent and rather sizeable literature suggests that obesity is an inflammatory response and other data link energy dysregulation to brain inflammation—specifically in the hypothalamus (Monteiro and Azevedo 2010; Thaler and Schwartz 2010). Inflammation can be a defensive response to environmental toxicants, suggesting that exposure to pesticides could be linked to obesity via inflammatory mechanisms. Brain inflammation has been described for several OPs (Lassiter *et al.* 2010).

In addition, energy regulation is based in part on the operation of hippocampal-dependent inhibitory learning and memory mechanisms that serve to control intake (Davidson *et al.* 2005; Gomez-Pinilla 2008; Liu *et al.* 2003). High energy diets (high in saturated fats and processed sugars) have been shown to degrade these types of cognitive control functions with the consequences being that animals are less able to refrain from responding to environmental cues that evoke intake (Kanoski and Davidson 2010; Parrott and Greenwood 2007). Failure to inhibit responding to these cues results in excessive energy consumption leading to positive energy balance. However, this aspect of hippocampal function is unexplored in toxicology and the literature has tended to behaviorally assess hippocampal functioning almost exclusively in terms of performance in spatial memory tasks (e.g., water maze) while ignoring the types of non-spatial hippocampal-dependent learning and memory functions that could play a role in maintaining energy balance. This possibility was raised by recent

findings with early-life exposure to parathion (Lassiter *et al.* 2010; Slotkin 2010; Slotkin *et al.* 2009a; Slotkin *et al.* 2009b). These animals displayed changes in neurotransmitter function and oxidative stress in the brain, many of which were *reversed* in animals that consumed a high fat diet. The neurotransmitter defects involved circuits that control cognition, mood and appetite, leading the authors to propose that the neurological deficits caused by early-life exposure to OPs might lead to a subsequent sub-conscience drive to "self-medicate" by consumption of a high-fat diet (Figure 6). Future research should focus on how events that happen at the molecular, cellular, or physiological levels of analysis are translated into changes in feeding, drinking, and/or energy expenditure.

Figure 6. High fat reverses neural deficits caused by OP exposure and this may provide a "subconscious drive" to consume an unhealthy diet



Changes in neurotransmitter function cased by neonatal treatment with parathion reversed when animals consumed a high fat diet (**A**, Slotkin et al., 2009) leading to the suggestion that the neurological deficits caused by early-life exposure to OPs might lead to a subsequent sub-conscience drive to "self-medicate" by consumption of a high-fat diet (**B**)

Table 6. Summary of study findings related to body weight, adiposity, and serum lipids following developmental exposure to nicotine

Study Design	Reference	Endpoint	Effect
gestation			
Sprague-Dawley rat pups received 0, 0.5 or 2.0 mg/kg diazinon or 0, 0.1 or 0.2 mg/kg-d parathion by sc injection on PND1-4. Animals were assessed at PND30, 60, and 100 and body weight was analyzed by MANOVA that incorporated all ages and both sexes	Adigun et al. (2010c)	diazinon, 0.5 mg/kg-d	
		body weight	↓
		diazinon, 2.0 mg/kg-d	
		body weight	↓
		parathion, 0.1 mg/kg-d	
		body weight	↔
		parathion, 0.2 mg/kg-d	
		body weight	↔
Sprague-Dawley rat pups received 0 or 1mg/kg-d chlorpyrifos by sc injection on PND1-4. Body weight assessed on PND110 and 120	Slotkin et al. (2005)	chlorpyrifos, 1 mg/kg-d	
		body weight	↔
		glucose (non-fasted)	↔
		insulin (non-fasted)	↑ ♂; ↔ ♀
		cholesterol	↑ ♂; ↔ ♀
		triglycerides	↑ ♂; ↔ ♀
		non-esterified free fatty acids	↔
		glycerol	↔
Sprague-Dawley rat pups received 0, 0.1 or 0.2 mg/kg-d parathion by sc injection on PND1-4. At 15 weeks of age, half the rats were switched to a high-fat diet (HFT) for 7 weeks.	Lassiter et al (2010)	parathion, 0.1 mg/kg-d	
		body weight, standard diet	↑ ♂; ↓ ♀
		body weight, HFD	↔ ♂; ↑ ♀
		leptin (fasted), standard diet	↑ ♂; ↔ ♀
		leptin (fasted), HFD	↑ ♂; ↔ ♀
		adiponectin, standard diet	↔
		adiponectin, HFD	↑ ♂; ↔ ♀
		parathion, 0.2 mg/kg-d	
		body weight, standard diet	↔ ♂; ↓ ♀
		body weight, HFD	↔ ♂; ↓ ♀
		leptin (fasted), standard diet)	↔
		leptin (fasted), HFD)	↔ ♂; ↓ ♀
		adiponectin, standard diet	↓ ♂; ↔ ♀
		adiponectin, HFD	↔
Sprague-Dawley rat pups received 0, 0.1 or 0.2 mg/kg-d parathion by sc injection on	Lassiter et al. (2008)	parathion, 0.1 mg/kg-d	
		standard diet	

Table 6. Summary of study findings related to body weight, adiposity, and serum lipids following developmental exposure to nicotine

Study Design	Reference	Endpoint	Effect
PND1-4. At 15 weeks of age, half the rats were switched to a high-fat diet for 7 weeks.		body weight	↑ male; ↑ female body weight through PND80; ↓ female body weight after PND84
		glucose (non-fasted)	↔
		insulin (fasted or non-fasted)	↔
		HbA1c	↔ ♂; ↓ ♀
		triglycerides	↔ (fed or fasted)
		cholesterol	↔ ♂; ↓ ♀ (collapsed across diets)
		NFEA	↔ ♂, ↑ ♀ (fasted state)
		high fat diet	
		body weight	↔ ♂; ↑ ♀
		glucose (non-fasted)	↔
		insulin (fasted or non-fasted)	↔
		HbA1c	↔ ♂; ↓ ♀
		triglycerides	↔
		cholesterol	↓ ♂; ↓ ♀s (collapsed across diets)
		NFEA	↔
		parathion, 0.2 mg/kg-d	
		standard diet	
		body weight	↔ ♂; ↑ ♀
		glucose (non-fasted)	↑
		insulin (fasted or non-fasted)	↔
		HbA1c	↓
		triglycerides	↔
		cholesterol	↔ ♂; ↓ ♀ (collapsed across diets)
		NFEA	↔ ♂, ↑ ♀(fasted state)
		high fat diet	
		body weight	↔ ♂; ↓ ♀
		glucose (non-fasted)	↔
		insulin (fasted or non-fasted)	↔
		HbA1c	↔ ♂; ↓ ♀
		triglycerides	↔
		cholesterol	↓ ♂; ↓ ♀ (collapsed across diets)
		NFEA	↔

Table 6. Summary of study findings related to body weight, adiposity, and serum lipids following developmental exposure to nicotine

Study Design	Reference	Endpoint	Effect
Sprague-Dawley rat pups received 0, 0.5 or 2.0 mg/kg-d diazinon by sc injection on PND1-4. On PND105 weeks of age, half the rats high-fat diet for 5 weeks and then returned to a normal diet for 2 more weeks.	Roegge et al. (2008)	diazinon, 0.5 mg/kg-d	
		standard diet	
		body weight	↔
		high fat diet	
		body weight	↑ ♂ and ♀
		diazinon, 2.0 mg/kg-d	
		standard diet	
		body weight	↔
		high fat diet	
		body weight	↔
Pregnant Long-Evans rats received chlorpyrifos by oral gavage at 0 or 2.5 mg/kg-d from GD7 – PND21. Body weight assessed in adulthood in two males and 2 females from each litter	Lassiter et al. (2008)	chlorpyrifos, 2.5 mg/kg-d	
		birth weight	↔
		body weight and growth through weaning	↔
		body weight, PND51 to PND101	↑ ♂; ↔ ♀
		body volume, PND101	↑ ♂; ↔ ♀
		leptin	↔
		leptin-weight correlation	weakened correlation in males (r=0.93 for control males vs. r=0.66 for treated males; eliminated correlation in females (r=0.87 for control females vs. r=0.44 for treated females)

1.4 Vacor

One of the most well-described "environmental" chemicals known to induce Type I diabetes in humans is Vacor, a rodenticide containing ~2% N-3-pyridylmethyl N'-p-nitrophenyl urea *(*PNU*)* (Gallanosa *et al.* 1981; Karam *et al.* 1980; Miller *et al.* 1978; Mindel 1986; Peters *et al.* 1981; Pont *et al.* 1979; Prosser and Karam 1978; Yoon 1990). Vacor is a substituted urea compound that has been causing pancreatic effects that have been described as being similar to alloxan and streptozotocin (Esposti *et al.* 1996), two other diabetogenic agents that contain a urea group and destroy pancreatic beta cells, presumably through impairment of mitochondrial function (Table 7). Both are glucose analogues that are selectively toxic to insulin-producing pancreatic beta cells because they preferentially accumulate in beta cells through uptake via the GLUT2 glucose transporter (Szkudelski 2001). The sale of Vacor was voluntarily stopped by its manufacturer, the Rohm and Hass Company, in 1979 after reports of accidental poisoning or suicidal ingestions in children and adults in the US and Korea (Gallanosa *et al.* 1981; LeWitt 1980; Mindel 1986). In adults, the ingestion often resulted in syndrome of severe diabetes with ketoacidosis, retinopathy[6], neuropathy, and persistent hyperglycemia accompanied by diabetic microangiopathy (Feingold *et al.* 1986; Karam *et al.* 1980; Lee *et al.* 1988; Siperstein 1988; Yoon 1990). Hyperglycemia is apparent within hours of poisoning and pancreatic beta cell damage is persistent. In addition, islet cell antibodies have been detected in some patients diagnosed with Vacor induced diabetes suggesting induction of an autoimmune response characteristic of Type I diabetes (Karam *et al.* 1980). Less serious outcomes were reported in cases that involved children, most of whom were treated with emetics and/or lavage (Gallanosa *et al.* 1981).

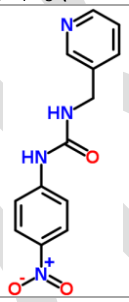
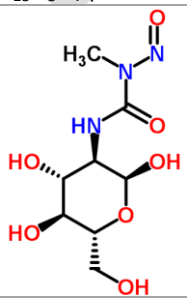
Animal and *in vitro* studies show that Vacor causes diabetes by destroying pancreatic β cells which leads to impaired glucose tolerance in rats (Lee *et al.* 1988), decreased insulin release in isolated rat pancreatic islet cells (Esposti *et al.* 1996; Taniguchi *et al.* 1989; Wilson and Gaines 1983) and hamster insulinoma HIT-T15 cells (Esposti *et al.* 1996), and reduced insulin staining in cultured fetal mouse pancreatic islet cells in the absence of major cellular damage (Myers *et al.* 1999). Using cultured pancreatic islets isolated from neonatal rats, Wilson and Gaines (1983) found the beta cells to be about 10-times more sensitive to Vacor than fibroblasts. Vacor may also cause destruction of glucagon producing α-cells (Kenney *et al.* 1981).

Vacor is an antagonist for reactions involving nicotinamide and has several effects on mitochondria that appear to contribute to its diabetogenic activity. It may cause increased activity of poly(ADP-ribose) synthetase by virtue of being nicotinamide antagonist which can lead to reduced NAD+ activity and impaired mitochondrial function (Szkudelski 2001). Simultaneous treatment with nicotinamide will attenuate effects of Vacor on insulin release in cultured rat pancreatic cells (Wilson and Gaines 1983) and nicotinamide has been used as a treatment in cases of human poisoning (Gallanosa *et al.* 1981; Johnson *et al.* 1980; Karam *et al.* 1980; Pont *et al.* 1979). The increase in activity of poly(ADP-ribose) synthetase seems to be a

[6] The degree of proteinuria and retinopathy in Vacor-diabetics has been reported as worse relative to "normal" diabetics (Feingold *et al.* 1986).

commonality with streptozotocin and alloxan and other compounds that cause oxidative stress attributed to their ability to generate DNA strand breaks and fragmentation caused by DNA alkylation and/or free radical production. In brief, DNA strand breaks increase activity of poly(ADP-ribose)synthetase, which can decrease NAD^+ concentrations. NAD+ is an enzyme cofactor that is reduced by extracting electrons from hydrogen atoms during the tricarboxylic acid (TCA) cycle (also called Krebs or citric acid cycle), and transports these electrons (as NADH) to the respiratory or electron transport chain located on the inner mitochondrial membrane. Thus, decreased levels of NAD+ slow the TCA cycle and diminish mitochondrial function. Other studies implicate mitochondrial toxicity and free radicals in mediating the diabetogenic effects of Vacor. Esposti et al. (1996) found that Vacor is a specific inhibitor of NADH:ubiquinone reductase activity of complex I of the mitochondrial respiratory chain at concentrations that lead to diminished insulin release from rat islets and hamster insulinoma HIT-T15 cells. Inhibition of complex I, such as by rotenone, can enhance reactive oxygen species (ROS) production from mitochondria in INS-1 (Pi *et al.* 2007). Thus, the specific inhibitory effect of Vacor on complex I could be a critical mechanism for Vacor-induced ROS production. Crouch et al (1981) found that Vacor, streptozotocin, and alloxan all inhibit activity of the enzyme superoxide dismutase (SOD), a scavenger of superoxide radicals present is islet cells isolated from rats and dogs.

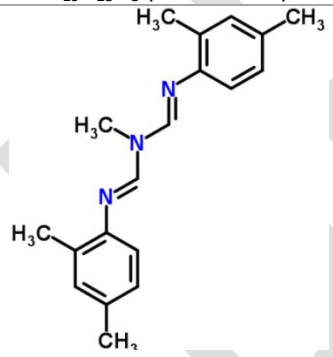
Table 7. Comparison of Vacor to other diabetogenic agents with urea groups (streptozotocin and alloxan)

Common name	**Vacor** (MeSH heading: pyriminil)	**Streptozocin (STZ)**	**Alloxan**
CAS number	53558-25-1	18883-66-4	50-71-5
Formula and molecular weight	$C_{13}H_{12}N_4O_3$ (MW 272.3)	$C_8H_{15}N_3O_7$ (MW 265.2)	$C_4H_2N_2O_4$ (MW 142.1)
Structure			
Use	Rodenticide marketed from 1975-1979, banned after reports in human poisoning	Used in research to produce animal models for Type 1 diabetes.	
Mechanisms	nicotinamide antagonist; inhibition of complex I in mitochondrial respiration chain (Esposti *et al.* 1996)	Generation of DNA strand breaks and fragmentation caused by DNA alkylation and/or free radical production which can lead to impairment of the TCA cycle and diminished mitochondrial function. Both are glucose analogues that are selectively toxic to insulin-producing pancreatic beta cells because they preferentially accumulate in beta cells through uptake via the GLUT2 glucose transporter. Alloxan diabetogenic effects have also been attributed to disruption of calcium homeostasis and inhibition of glucokinase activity , a “glucose sensing” enzyme important in regulating insulin secretion (Szkudelski 2001; Wang and Gleichmann 1998)	

It is not known if Vacor is operating through other mechanisms implicated in the diabetogenic effects of STZ and alloxan. The stimulatory effect of STZ on the production of nitric oxide (NO), an important reactive oxygen and nitrogen species (ROS/RNS), is an important mechanism for STZ toxicity. On the mechanism(s) of alloxan action in beta-cells, alloxan-dialuric acid redox cycle, could be an important resource of reactive oxygen species (ROS) production (Szkudelski 2001) as is the case for quinone compounds (Taguchi *et al.* 2007). One question is whether Vacor can induce ROS production by similar mechanisms.

1.5 Amitraz

Amitraz is a formamidine insecticide that has been reported to cause hyperglycemia in children (Caksen *et al.* 2003; Ertekin *et al.* 2002; Kennel *et al.* 1996; Ulukaya *et al.* 2001; Yilmaz and Yildizdas 2003) and adults (Elinav *et al.* 2005; Kennel *et al.* 1996; Ulukaya *et al.* 2001) following accidental or deliberate poisoning. When present, the hyperglycemia usually resolves within days. There seems to be a higher incidence of amitraz poisoning in certain regions, in particular rural areas of Turkey among families raising animals (Ertekin *et al.* 2002; Ulukaya *et al.* 2001; Yilmaz and Yildizdas 2003). Amitraz has also been shown to cause hyperglycemia in dogs (Hsu and Schaffer 1988; Hugnet *et al.* 1996) and worker honeybees (Cascino *et al.* 1989) and impaired glucose tolerance in rats (Smith *et al.* 1990). The hyperglycemia in dogs and impaired glucose tolerance in rats is accompanied by hypoinsulinemia (Hsu and Schaffer 1988; Hugnet *et al.* 1996; Smith *et al.* 1990). No effect on glucose was found in a study in mice treated with a single administration of 15 or 45 mg/kg amitraz by gavage although the authors noted that the vehicle control DMSO caused a significant reduction in serum glucose compared to the water control group and thus might have masked any hyperglycemica effect of amitraz (Filazi *et al.* 2003).

Amitraz
33089-61-1
$C_{19}H_{23}N_3$ (MW 293.41)

Use: Insecticide and acaricide used to control red spider mites, leaf miners, scale insects, and aphids. On cotton it is used to control bollworms, white fly, and leaf worms. On animals it is used to control ticks, mites, lice and other animal pests.
Mechanism: α2-adrenoreceptors agonist, inhibition of the enzyme monoamine oxidase.

Decreases in insulin release are also found using *in vitro* models. Abu-Basha et al. (1999) reported that amitraz and its active metabolite, BTS 27271(Corta *et al.* 1999) , inhibited insulin secretion from perfused rat pancreatic tissue in a concentration dependent manner at 0.01, 0.1, 1 or 10 µM. Both compounds also increased glucagon secretion (amitraz at 10 µM and BTS 27271 at 1 and 10 µM). Similar findings were reported by Chen and Hsu (1994) using the rat RINm5F β-cell line. Insulin release induced by the phosphodiesterase inhibitor IBMX (3-isobutyl-1-methylxanthine) was inhibited by both amitraz (1 and 10µM) and BTS 27271 (0.01, 1, 10 µM).

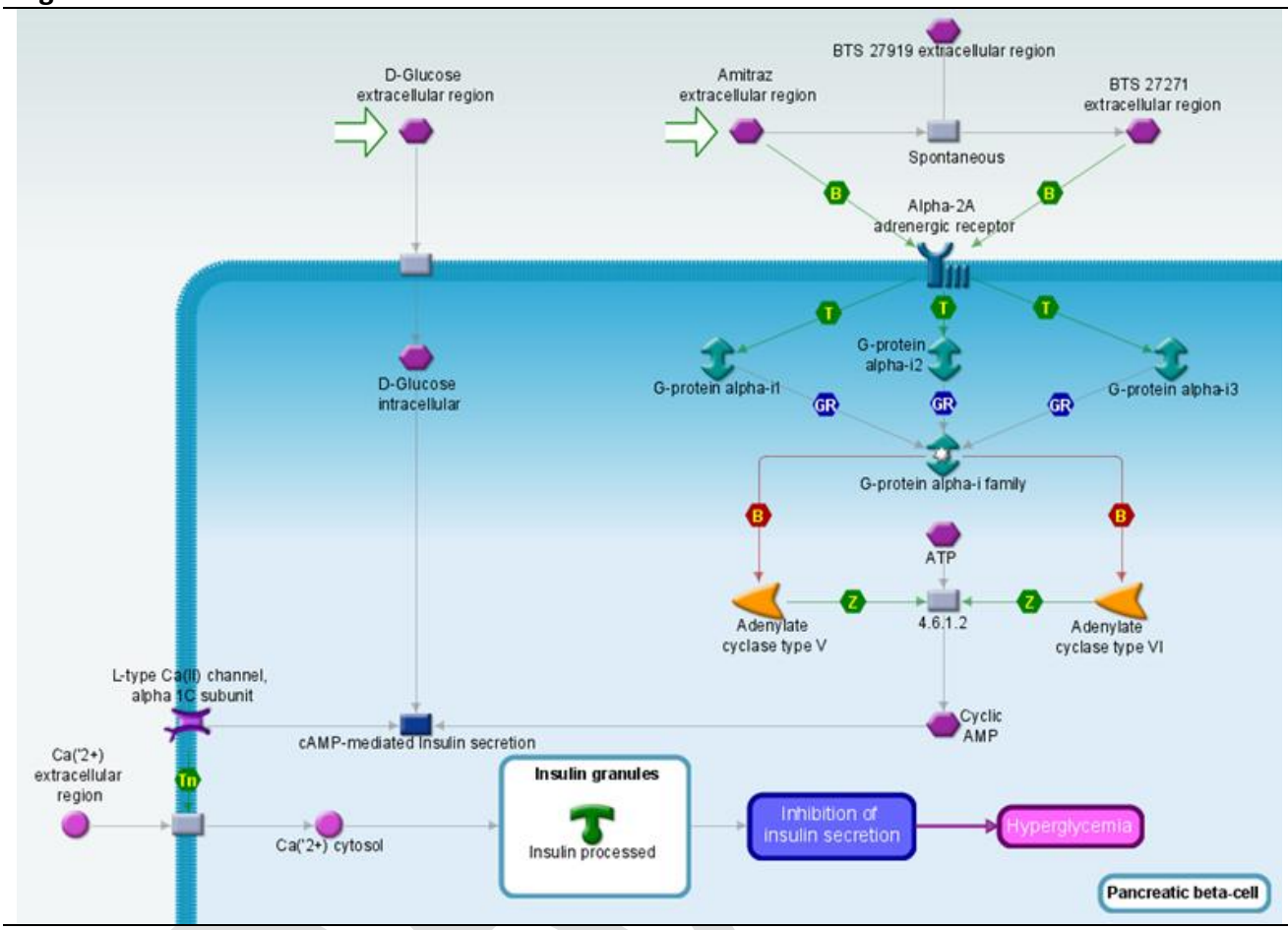
The effects of amitraz on glucose are attributed to activation of α-2 adrenoreceptors which suppress insulin secretion when activated. Administration of α-2 receptor antagonists, such as yohimbine and atipamezole, block amitraz induced hypoinsulinemia and/or hyperglycemia (Chen and Hsu 1994; Hugnet *et al.* 1996; Smith *et al.* 1990). An antagonists for the α-1 adrenoceptor, prazosin, did not cause a similar effect (Chen and Hsu 1994; Smith *et al.* 1990). Based on *ex vivo* and *in vitro* studies the active metabolite of amitraz, BTS 27271, appears more potent than the parent compound as it inhibits insulin release and increased glucagon secretion at concentrations at least 10-fold lower than amitraz (Abu-Basha *et al.* 1999; Chen and Hsu 1994). Similar to the parent compound, BTS 27271-induced hypoinsulinemia is prevented by co-administration of an α-2-receptor antagonist (yohimbine), but not the α-1-receptor antagonist prazosin (Chen and Hsu 1994).

A schematic of how amitraz and its metabolite BTS 27271 inhibit insulin secretion is presented Figure 7. These compounds can activate α2A adrenergic receptor signaling to through G-protein alpha-i1, G-protein alpha-i2 and G-protein alpha-i3 (Abu-Basha *et al.* 1999; Chen and Hsu 1994; Kowluru *et al.* 1996; Schmidt *et al.* 1991). The G-protein alpha-i family inhibits adenylate cyclase type V and adenylate cyclase type VI (Leech *et al.* 1999), and leads to a loss of cyclic AMP production. Alpha-2A adrenergic receptor-mediated inhibition of cyclic AMP promotes the suppression of L-type Ca(II) channel, alpha 1C subunit (Suga *et al.* 2004), resulting in lower levels of Ca('2+) in the cytosol, inhibition of D-glucose-induced insulin secretion (see negative regulation of Insulin secretion) and hyperglycemia (Abu-Basha *et al.* 1999; Chen and Hsu 1994).

In Phase 1 of ToxCast, amitraz was active for α-2A and α-2b adrenergic receptors (Table 8). Amitraz was not active on assays for adrenergic,α-2C-, receptor (ADRA2C), adrenergic,β-1-, receptor (ADRBI), adrenergic, β-2-, receptor, surface (ADRB2), adrenergic, β-3-, receptor (ADRB3). Amitraz was not linked to diabetes in the Comparative Toxicogenomics Database (CTD),[7] which may reflect an absence of gene-centric data for this pesticide.

[7] The Comparative Toxicogenomics Database (CTD),[7] is a community-supported public resource being developed at the Mount Desert Island Biological Laboratory (MDIBL), with support from the National Institutes of Environmental Health Sciences (NIEHS) (ES014065) and the National Center for Research Resources (NCRR) (RR016463) of the National Institutes of Health (NIH). CTD includes manually curated data describing cross-species chemical–gene/protein interactions and chemical– and gene–disease relationships to illuminate molecular mechanisms underlying variable susceptibility and environmentally influenced diseases. Website: http://ctd.mdibl.org/.

Figure 7. Amitraz-induced inhibition of insulin secretion



Draft text and schematic prepared by GeneGo. See background document "MCLegend.pdf" for figure legend

Table 8. Pattern of screening data for Amitraz and other chemicals tested in Phase 1 of ToxCast™ that interacted with same assay targets[1]

CASRN	Name	adrenergic receptor, α-2A (ADRA2A)	adrenergic receptor, α-2A (Adra2a)	monoamine oxidase A (NVS ENZ rabI2C)	serotonin receptor 7 (HTR7)	adrenergic receptor, α-2b (Adra2b)	serotonin receptor 1A (Htr1a)
33089-61-1	Amitraz	0.05	0.06	0.16	0.45	1.03	1.8
43222-48-6	Difenzoquat metilsulfate	1.07	3.18	27.1	47.1	0.59	
155569-91-8	Emamectin benzoate	21.3	20.8		4	23.5	
68157-60-8	Forchlorfenuron	22.1	40		48.5		
67747-09-5	Prochloraz		1.83		39.4	4.7	
118134-30-8	Spiroxamine	6.82	29.7		14.4		
119446-68-3	Difenoconazole		2.36			29.5	
76-87-9	Fentin	5.79			0.2		
35554-44-0	Imazalil			42.4		12.4	
87820-88-0	Tralkoxydim	21.8				7.41	
2971-36-0	2,2-Bis(4-hydroxyphenyl)-1,1,1-trichloroethane (HPTE)				8.85		
71751-41-2	Abamectin				4.7		
314-40-9	Bromacil				47.2		
133-06-2	Captan				44.9		
120-32-1	Clorophene				16.5		
210880-92-5	Clothianidin					29.6	
120116-88-3	Cyazofamid					22.7	
52315-07-8	Cypermethrin				42.5		
85509-19-9	Flusilazole				38.8		
23422-53-9	Formetanate hydrochloride			1.94			
79983-71-4	Hexaconazole				41.9		
8018-01-7	Mancozeb		41.3				
51596-11-3	Milbemectin				6.84		
1763-23-1	Perfluorooctane sulfonic acid				17.8		
2312-35-8	Propargite				37.7		
10453-86-8	Resmethrin				41.5		
21564-17-0	TCMTB	37.3					
148-79-8	Thiabendazole			40.8			

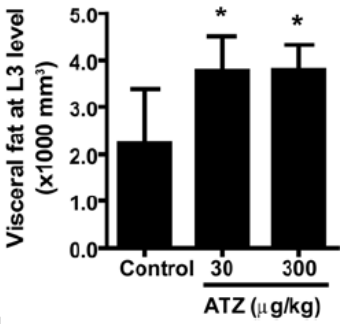
[1]Data presented as active concentration (AC_{50}) in µM. Based on assay targets most relevant for effects on glucose control (i.e., excludes whole cell toxicity, genes involved in immune/inflammation)

1.6 Other pesticides

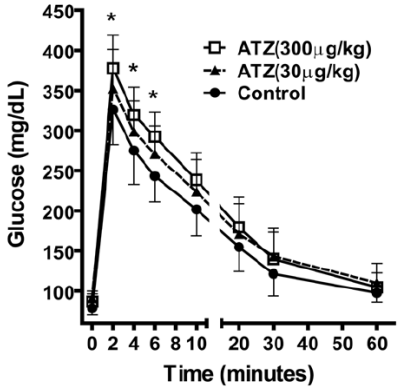
A relatively large literature exists on OPs reporting hyperglycemia and pancreatic effects in laboratory animals (discussed above) and for organochlorine pesticides and diabetes in humans (discussed in the POPs chapter). Far less experimental data exist for the other pesticides. One recent study by Lim et al. (2009) reported that atrazine caused increased body weight and intra-abdominal fat, reduced insulin sensitivity, and mitochondrial dysfunction in male Sprague-Dawley rats that drank 30 or 300 µg/kg-day for 5 months (8 rats/group). Body weight and adiposity were assessed in animals fed a standard diet as well as animals fed a high fat diet (40% fat) for the last 2 months of treatment. The atrazine animals in the 300 µg/kg-day fed a standard diet weighed ~5% more than controls at the end of the 5 month treatment period. Body weight was significantly increased in both the 30 and 300 µg/kg-day treatment groups compared to controls in animals fed a high fat diet by 8.8% and 9.8%, respectively. The atrazine-treated animals in both dose groups fed a high fat diet also had more central visceral fat than control animals (Figure 8, panel A). Fasting glucose levels in the atrazine treated rats (both dose groups) were statistically higher compared to controls, but still within the normal range (86.5 to 102 mg/dL). Impaired glucose tolerance in the IVGTT and reduced insulin sensitivity index was found in both

Figure 8

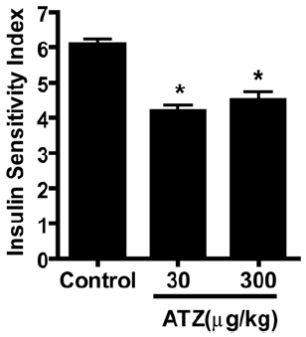
A. Increased visceral fat at the upper margin of the L3 vertebra in 0 and 300 µg/kg-day atrazine (AZT) treatment groups fed a high fat diet (measured by horizontal CT scan and imaged with a Hounsfield unit).



B. Changes in plasma glucose during IVGTT. Fasting glucose levels were also higher in the AZT treated animals, but still within the normal range (86.5 to 102 mg/dL)



C. Reduced insulin sensitivity index in AZT-treated rats. Insulin sensitivity was calculated by using data from the hyperinsulinemic-euglycemic clamp study, a test designed to measure an animal's ability to maintain glucose levels when challenged with a high insulin load. Specifically, the insulin sensitivity index was calculated by dividing the steady-state glucose infusion rate by the mean insulin concentration during the 90–120-minute clamping window and expressed as mg glucose kg21 minute21 of for each ng/mL of insulin.



From Lim et al. (2009) an open access article.

treatment groups (Figure 8, panels B and C).

There was no different in food intake or physical activity in the animals, but decreased energy metabolism was described based on reduced energy expenditure (measured by indirect caloric measurements) and oxygen consumption rates measured in mitochondria isolated from the soleus muscle of the atrazine-treated rats. Those findings, combined with results of other *in vitro* studies using L6 muscle cells, indicated that atrazine could interfere with ubiquinone (Q) binding sites between complex I and III, or II and III. The mitochondrial in skeletal muscle and liver from the rats were described as being swollen with abnormal cristae. The effects on visceral fat, glucose tolerance, insulin sensitivity and mitochondrial toxicity have not been assessed for atrazine before. Body weight has, and this is the first study reporting an increase. The authors suggested previous findings of decreased or unchanged body weight could be due to the higher dose levels used in those studies (2,700 to 50,000 µg/kg-d versus 30 and 300 µg/kg-d). Atrazine also increases aromatase activity to result in increased production of estrogen (Higley *et al.* 2010; Holloway *et al.* 2008; Tinfo *et al.* 2010). This activity of atrazine is important to consider in future research as estrogen is important in regulating glycemic control, pancreatic function, and body weight, albeit through complex pathways that involve differential effects of interactions with classic estrogen receptors (ERα, ERβ) as well as non-classical ER activities, receptor-specific effects (Foryst-Ludwig and Kintscher 2010; Liu and Mauvais-Jarvis 2009; Mauvais-Jarvis 2011; Musatov *et al.* 2007).

TofRef

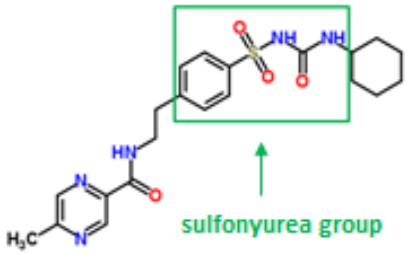
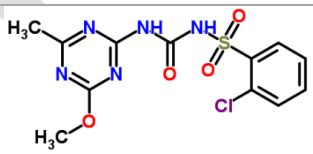
Table 9 and presents the search results from a ToxRefBD query for chemicals that caused increased body weight (or body weight gain), increased glucose, and pancreatic effects. Most of the chemicals are pesticide active ingredients and were also tested in Phase 1 of ToxCast™. A version of this table in Excel format with hyperlinks to the ToxCast™ screening data + common names for gene-based assay targets is available in Appendix B.

Four of the search results were for sulfonylurea herbicides and 3 of the 4 caused pancreatic effects. This finding is interesting because sulfonylureas herbicides are structurally similar to sulfonylurea derivatives used to type 2 diabetes (Figure 9). In plants, sulfonylureas act to inhibit amino acid synthesis via inhibition of acetolactic acid synthase. Sulfonylurea herbicides are generally considered to exhibit low mammalian toxicity and their use has increased extensively over the past two decades (USGS). The application rates are also generally low for these herbicides which allow them to be applied at concentrations that often fall below limits of detection in environmental samples (USGS). As pharmaceuticals, sulfonylurea derivatives help control diabetes by increasing insulin secretion from β cells which results in a lowering of blood glucose. More specifically, sulfonylureas bind with high affinity to the sulfonylurea receptor-1 subunit (SUR1) of the ATP-sensitive potassium channel [K(ATP)] in pancreatic beta cells (Thevenod 2002). Sulfonylurea binding causes K(ATP) channels to close, reducing potassium conductance and leads to membrane depolarization. The membrane depolarization leads to opening of calcium channels and entry of Ca^{+2} ions into the β cell, which then triggers insulin

secretion and subsequent decreased blood glucose levels. One of the side effects with sulfonylureas in practice is hypoglycemia. The stimulation of insulin secretion by sulfonylureas while good in the short term may cause pancreatic damage due to overstimulation, which may cause reactive oxygen species, endoplasmic reticulum stress, mitochondrial dysfunction, and β cell death (Remedi and Nichols 2008)

Aside from the studies presented in Table 9, no other studies evaluating the impacts on glycemic control or pancreatic function were identified for sulfonylurea herbicides in the 5630 references that were initially retrieved in the PubMed search used to identify the relevant literature for this workshop. Three of the 4 sulfonylurea herbicides in Table 9 were included in Phase 1 of ToxCast™. The more commonly detected sulfonylurea in streams and reservoirs are not represented in ToxCast (USGS). In general, the sulfonylurea pesticides were relatively inactive on gene-based targets in ToxCast. ToxCast does not include coverage for SUR1 but does includes a binding assay for the potassium inwardly rectifying channel, subfamily J, member 11 (Kcnj11, assay name NVS_IC_rKATPCh) . None of the sulfonylurea herbicides displayed activity for this target, although one other pesticide did that is also included in Table 9 (3-Iodo-2-propynylbutylcarbamate, CASRN 55406-53-6). This carbamate fungicide was shown to cause pancreatic effects in a 2-year cancer bioassay study (Mulhern *et al.* 1989; Tzoulaki *et al.* 2009).

Figure 9

Glipizide	Chlorsulfuron
29094-61-9	64902-72-3
$C_{21}H_{27}N_5O_4S$ (MW 445.54)	$C_{12}H_{12}ClN_5O_4S$ (MW 357.77)
	
Use: Antidiabetogenic drug used to treat type 2 diabetes	**Use:** Class of herbicides
Mechanism as an anti-diabetogenic agent: Increases insulin release from beta cells by binding to ATP-dependent K^+ (K_{ATP}) channel on the cell membrane of pancreatic beta cells. The K_{ATP} channel is a complex of the inward-rectifier potassium ion channel $K_{ir}6.2$ and sulfonylurea receptor SUR1	**Mechanism as an herbicide:** Inhibits amino acid synthesis via inhibition of acetolactic acid synthase

Similarly, another pesticide included in Table 9, imazalil, belongs to the same general imidazole chemical class as agents either used to manage diabetes or being researched for their value as therapeutic agents. Imazalil caused pancreatic effects and elevated glucose in two separate studies. Imazalil would likely have been hypothesized to affect the pancreas based on ToxCast™ screening data based on its interactions receptor systems involved in mediating pancreatic

function, including several cholinergic muscarinic receptors (AC_{50}s of 3.9 – 11.5 µM), adrenergic receptor 2β (AC_{50} = 12.4 µM), PPARγ (AC_{50} = 12.4 µM), and RXRα (AC_{50} = 3.8 µM).

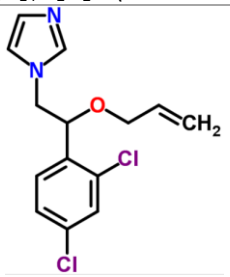
Imazalil
35554-44-0
$C_{14}H_{14}Cl_2N_2O$ (MW 297.18)

Use: Fungicide
Mode of action: Affect the cellular permeability of yeast; inhibition of cell membrane functions, inhibits ergosterol biosynthesis in fungal cells

Table 9. ToxRef search results for chemicals that caused increased body weight (or body weight gain), increased glucose, or pancreatic effects. Those shaded red were tested in Phase 1 of ToxCast™ (hyperlink access data from EPA website, see also Appendix B for screening data + common names for gene-based assay targets)

Chemical and CASRN	Chemical Class	Study Design*	Doses Tested (mg/kg-d)		Effect Doses (mg/kg-d)			Citation
			Lowest	Highest	↑ Body Weight	↑ Glucose	Pancreatic Pathology or Neoplasia	
Cymoxanil (57966-95-7)	aliphatic nitrogen	CHR, rat, feed	1.98	126			126	(Cox 1994b)
Cymoxanil (57966-95-7)	aliphatic nitrogen	CHR, mouse, feed	4.19	582			582	(Cox 1994a)
Acetochlor (34256-82-1)	amide	CHR, rat, feed	0.67	92.1			92.1	(Broadmeadow 1988)
Propyzamide (23950-58-5)	amide	SUB, rat, feed	2.5	289.2			254	(Anderson *et al.* 1989)
Abamectin (71751-41-2)	antibiotic	CHR, rat, feed	0.7	2.1	0.7			(Gordon 1985)
Emamectin benzoate (155569-91-8)	antibiotic	CHR, rat, feed	0.25	2.55	1.01			(Lankas 1994)
Azoxystrobin (131860-33-8)	antibiotic	SUB, rat, feed	20.4	448.6		223	444	(Milburn 1992)
Dicamba (1918-00-9)	aromatic acid	CHR, rat, feed	2.5	125	125			(Goldenthal 1985)
Quinclorac (84087-01-4)	aromatic acid	CHR, rat, feed	56	757			487	(Schilling 1988)
Ethofumesate (26225-79-6)	benzofuranyl alkylsulfonate	CHR, rat, feed	97	1466		332	1470	(Everett *et al.* 1991)
Diphenylamine (122-39-4)	bridged diphenyl	SUB, rat, feed	9.6	1323.8		650		(Krohmer 1992)
Carbofuran (1563-66-2)	carbamate	MGR, rat, feed	1	5	1			(EPA)
3-Iodo-2-propynylbutylcarbamate (55406-53-6)	carbamate	CHR, rat, feed	20.1	80.8			80.1	(Mulhern *et al.* 1989)
Sodium Dimethyldithiocarbamate (128-04-1)	carbamate	SUB, rat, gavage/intubation	0.5	250		250	250	(Marquis 1991)
Bifenazate (149877-41-8)	carbazate	CHR, rat, feed	1	9.7	1.2			(Ivett 1999)
Tetraconazole (112281-77-3)	conazole	SUB, rat, feed	0.7	28.7	23.9			(Mayfield *et al.* 1988b)
Propiconazole (60207-90-1)	conazole	CHR, rat, feed	3.6	100.6			18.1	(Hunter *et al.* 1982)
Sethoxydim (74051-80-2)	cyclohexene oxime	CHR, mouse, feed	4.48	142.85		4.85		(Takaori *et al.* 1981)
Tepraloxydim (149979-41-9)	cyclohexene oxime	CHR, rat, feed	5	272			272	(Mellert *et al.* 1997)
Halofenozide (112226-61-6)	diacylhydrazine	SUB, rat, feed	0.07	54.61		52.7		(Anderson *et al.* 1995)
Captafol (2425-06-1)	dicarboximide	SUB, rat, feed	174	174	174			(Brorby 1986)
Famoxadone (131807-57-3)	dicarboximide	CHR, mouse, feed	0.701	392			392	(Mackenzie 1996)
Flumioxazin (103361-09-7)	dicarboximide	SUB, rat, feed	1.9	218.4			218	(Adachi 1991)
Vinclozolin (50471-44-8)	dicarboximide	SUB, rat, feed	3.6	219			24	(Mellert 1993)
Vinclozolin (50471-44-8)	dicarboximide	CHR, rat, feed	2.3	180			23	(Mellert 1994b)
Vinclozolin (50471-44-8)	dicarboximide	CHR, rat, feed	7	257			7	(Mellert 1994a)
Ethalfluralin (55283-68-6)	dinitroaniline	CHR, rat, feed	5	125		5		(Adams *et al.* 1981)
Thiram (137-26-8)	dithiocarbamate	CHR, rat, feed	1.5	18.6			7.3	(Kehoe 1991)
Ziram (137-30-4)	dithiocarbamate	CHR, rat, feed	2.5	34.6			7.7	(Powell *et al.* 1994)
Imazalil (35554-44-0)	imidazole	SUB, rat, feed	1.25	60		3.75		(Lina *et al.* 1983)
Imazalil (35554-44-0)	imidazole	CHR, mouse, feed	6.67	110			88	(Verstraeten 1993)

Table 9. ToxRef search results for chemicals that caused increased body weight (or body weight gain), increased glucose, or pancreatic effects. Those shaded red were tested in Phase 1 of ToxCast™ (hyperlink access data from EPA website, see also Appendix B for screening data + common names for gene-based assay targets)

Chemical and CASRN	Chemical Class	Study Design*	Doses Tested (mg/kg-d)		Effect Doses (mg/kg-d)			Citation
			Lowest	Highest	↑ Body Weight	↑ Glucose	Pancreatic Pathology or Neoplasia	
Triflumizole (68694-11-1)	imidazole	CHR, rat, feed	3.5	77			59.4	(Broadmeadow *et al.* 1984)
Cyanamide (420-04-2)	inorganic	CHR, rat, gavage/intubation	1	7.5	7.5			(Osheroff 1991b)
Novaluron (116714-46-6)	insect growth regulators	CHR, mouse, feed	3.6	913.4	63.3			(Thirlwell 2000)
Novaluron (116714-46-6)	insect growth regulators	SUB, rat, [not Specified],	4.2	1820.6	819			(East 1998)
Pyriproxyfen (95737-68-1)	insect growth regulators	SUB, rat, feed	23.49	783.96		27.7		(Kogiso 1990)
Tebufenozide (112410-23-8)	insect growth regulators	SUB, rat, feed	1.3	1651		1650		(Osheroff 1991a)
Dimethomorph (110488-70-5)	morpholine	CHR, rat, feed	8.8	132.5			133	(Everett *et al.* 1988)
Azamethiphos (35575-96-3)	organophosphorus	CHR, mouse, feed	6.2	614.3			614	(Goodyer 1987)
Dichlorvos (62-73-7)	organophosphorus	CHR, rat, gavage/intubation	4	8			8	(Chan 1987)
Dimethoate (60-51-5)	organophosphorus	CHR, rat, feed	0.05	5			1.25	(Squire 1988)
Disulfoton (298-04-4)	organophosphorus	CHR, mouse, feed	0.15	2.4	2.4			(Mobay Chemical Corp. 1983)
Fenthion (55-38-9)	organophosphorus	CHR, mouse, feed	0.03	10.63	1.95			(Leser and Suberg 1990)
Fenthion (55-38-9)	organophosphorus	MGR, rat, feed	0.05	5	5			(Kowalski *et al.* 1989)
Malathion (121-75-5)	organophosphorus	CHR, rat, feed	4	868			29	(Daly 1996)
Parathion-methyl (298-00-0)	organophosphorus	CHR, mouse, feed	0.2	13.7	9.2			(Eiben 1991)
Propetamphos (31218-83-4)	organophosphorus	CHR, rat, feed	0.376	7.602			0.689, 7.6 (n)	(Luginbuehl 1980)
Tebupirimfos (96182-53-5)	organophosphorus	CHR, mouse, feed	0.52	43.57	38.8	38.8		(Eiben 1990)
Tebupirimfos (96182-53-5)	organophosphorus	SUB, rat, feed	0.2	4.9		0.4		(Eiben 1989)
Tribufos (78-48-8)	organophosphorus	CHR, mouse, feed	1.64	63.04	48			(Hayes 1989)
Perfluorooctanoic acid (PFOA), ammonium salt (335-67-1)	perfluorinated	CHR, rat, feed	15	15			15	(Biegel *et al.* 2001)
Clodinafop-propargyl (105512-06-9)	phenoxy	SUB, rat, feed	0.13	71.1		70		(Fankhauser 1989)
Fluazifop-butyl (69806-50-4)	phenoxy	CHR, rat, feed,	0.1	16	0.127			(Amyes *et al.* 1985)
Fluazifop-butyl(69806-50-4)	phenoxy	MGR, rat, feed	0.74	21.7	21.7			(Willoughby *et al.* 1981)
MCPA (94-74-6)	phenoxy	CHR, rat, feed	1.1	23	23			(Kirsch 1986)
Quizalofop-ethyl (76578-14-8)	phenoxy	CHR, mouse, feed	0.3	48	12			(Burdock *et al.* 1985)
Fipronil-desulfinyl (205650-65-3)	phenylpyrazole	CHR, rat, feed	0.025	0.546	0.546			(Bigot 1998)
Glyphosate (1071-83-6)	phosphonoglycine	SUB, rat, feed	63	1623		63	1270	(Stout and Johnson 1987)
Fipronil (120068-37-3)	pyrazole	SUB, rat, feed	0.07	24.03		0.37		(Holmes 1993)
Tebufenpyrad (119168-77-3)	pyrazole	CHR, rat, feed	0.21	16.95			13.4	(Mitchell 1992)
Tebufenpyrad (119168-77-3)	pyrazole	SUB, rat, feed	0.7	32	29			(Mitchell 1991)
Cypermethrin (52315-07-8)	pyrethroid	SUB, rat, feed	0.6	65.2			55.7	(McCarty 1990)

Table 9. ToxRef search results for chemicals that caused increased body weight (or body weight gain), increased glucose, or pancreatic effects. Those shaded red were tested in Phase 1 of ToxCast™ (hyperlink access data from EPA website, see also Appendix B for screening data + common names for gene-based assay targets)

Chemical and CASRN	Chemical Class	Study Design*	Doses Tested (mg/kg-d)		Effect Doses (mg/kg-d)			Citation
			Lowest	Highest	↑ Body Weight	↑ Glucose	Pancreatic Pathology or Neoplasia	
Resmethrin (10453-86-8)	pyrethroid	CHR, mouse, [not Specified],	36.3	165.8			138	(Knickerbocker *et al.* 1979)
Picloram (1918-02-1)	pyridine	CHR, rat, feed	20	200	20			(Landry *et al.* 1986)
Dithiopyr (97886-45-8)	pyridine	MGR, rat, feed,	1.7	230	187			(Ebino 1989)
Fluroxypyr (69377-81-7)	pyridine	MGR, rat, feed,	100	1000	750			(Vedula *et al.* 1996)
Dithiopyr (97886-45-8)	pyridine	DEV, rat, gavage/intubation	30	1000	1000			(Suzuki 1987)
Dithiopyr (97886-45-8)	pyridine	SUB, rat, feed,	0.606	379		379		(Harada 1986)
Fluazinam (79622-59-6)	pyridine	CHR, rat, feed	0.04	53			4.9	(Mayfield *et al.* 1988a)
Thiazopyr (117718-60-2)	pyridine	CHR, rat, feed	0.04	177.1			177	(Naylor and Mcdonald 1992)
Cyprodinil (121552-61-2)	pyrimidine	CHR, mouse, feed	1.08	630			212	(Frankhauser 1994)
Pyrimethanil (53112-28-0)	pyrimidine	CHR, mouse, feed	2	253.8			254	(Clay 1992)
Fludioxonil (131341-86-1)	pyrrole	CHR, mouse, feed	1.1	417			417	(Chang and Wyand 1993)
Dimethyldidecylammonium chloride (7173-51-5)	quaternary ammonium compound	MGR, rat, feed	15	75	75			(PMRA 1991)
Trifloxystrobin (141517-21-7)	strobilurin	SUB, rat, feed	6.44	618		618	127	(Gerspach 1995)
Oxasulfuron (144651-06-9)	sulfonylurea	CHR, rat, feed	0.84	871			425	(Pettersen and Morrissey 1996)
Sulfosulfuron (141776-32-1)	sulfonylurea	CHR, rat, feed	2.4	1296.5			244	(Naylor and Ruecker 1997)
Triasulfuron (82097-50-5)	sulfonylurea	SUB, rat, feed	10	1000		1000		(Tai 1985)
Tribenuron-methyl (101200-48-0)	sulfonylurea	CHR, rat, feed	1.25	62.5			62.5	(Tobia 1987)
Spirodiclofen (148477-71-8)	tetronic acid	CHR, mouse, feed	4.1	1495			1220	(Whale 2000)
Bentazone (25057-89-0)	thiodiazine	CHR, mouse, feed	15	300			60	(Takehara 1982)
Anilazine (101-05-3)	triazine	SUB, rat, feed	38.5	698.9			155	(Goodyer 1981)
Hydroxyatrazine (2163-68-0)	triazine	CHR, rat, feed	0.388	22.3			17.4	(Chow 1995)
Diniconazole (83657-24-3)	triazole	SUB, rat, feed	0.71	233	0.71	233		(Murakami *et al.* 1984)
Sulfentrazone (122836-35-5)	triazolone	SUB, rat, feed	3.3	534.9			199	(Nye 1993)
Pyridaben (96489-71-3)	unclassified	SUB, rat, feed	2.3	27.68	25.7			(Holmes 1988)
5,5-Dimethylhydantoin (77-71-4)	unclassified	SUB, rat, gavage/intubation	102	1019	1020			(Federici 1991)
5,5-Dimethylhydantoin (77-71-4)	unclassified	CHR, rat, feed	100	1000		320		(Naas 1996)
Acequinocyl (57960-19-7)	unclassified	CHR, rat, feed	2.25	93.56			2.92	(Inoue 1997)
Acibenzolar-S-Methyl (135158-54-2)	unclassified	CHR, mouse, feed	1.14	698			237	(Fankhauser 1996)
Bispyribac-sodium (125401-92-5)	unclassified	MGR, rat, feed	1.5	874	874			(Schardein 1994)

Table 9. ToxRef search results for chemicals that caused increased body weight (or body weight gain), increased glucose, or pancreatic effects. Those shaded red were tested in Phase 1 of ToxCast™ (hyperlink access data from EPA website, see also Appendix B for screening data + common names for gene-based assay targets)

Chemical and CASRN	Chemical Class	Study Design*	Doses Tested (mg/kg-d)		Effect Doses (mg/kg-d)			Citation
			Lowest	Highest	↑ Body Weight	↑ Glucose	Pancreatic Pathology or Neoplasia	
Bispyribac-sodium (125401-92-5)	unclassified	SUB, rat, feed	7.2	1582.5	1460			(Inoue 1991)
Cimecticarb (95266-40-3)	unclassified	MGR, rat, feed	0.59	1484.9	1480			(PMRA *et al.* 1991)
Cinmethylin (87818-31-3)	unclassified	CHR, rat, [not Specified],	1.5	150			150	(Dix 1985)
Fluthiacet-methyl (117337-19-6)	unclassified	CHR, rat, feed	0.2	368			130, 219 (n)	(Potrepka and Richter 1995)
Methyl iodide (74-88-4)	unclassified	MGR, rat, whole body	5	50	50			(Nemec 2003)
Prothioconazole-desthio (120983-64-4)	unclassified	MGR, rat, feed	2.48	51.9	51.9			(PMRA 2001)
Spiroxamine (118134-30-8)	unclassified	SUB, rat, feed	1.9	75.1	54.9			(Eiben and Hartmann 1992)
Triclosan (3380-34-5)	unclassified	MGR, rat, feed	15	150	50			(Morseth 1988)
Topramezone (210631-68-8)	unclassified	SUB, rat, feed	1.1	2.5			2.1	(Kaspers *et al.* 2003a)
Topramezone (210631-68-8)	unclassified	CHR, rat, feed	0.4	524.1			4.7	(Kaspers *et al.* 2003b)

*CHR = chronic; SUB = subchronic; MGR = multigenerational study

Appendix Tables

(version updated January 3, 2011)

1.7 Appendix A

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
Adult male Wistar rats received malathion in the diet at 0, 100, 200 or 400 ppm (estimated to be 0, ~5, ~10 or ~20 mg/kg-d) for 28 days. Also presented in study, but not summarized here: NA	6/group	0	Control (diet)	(Abdollahi *et al.* 2004)
		~5 mg/kg-d malathion	↑ Plasma glucose (1.25-fold) ↑ Hepatic PEPCK activity (1.25-fold) ↑ Hepatic GP (1.22-fold)	
		~10	↑ Plasma glucose (1.17-fold) ↑ Hepatic PEPCK activity (1.16-fold) ↑ Hepatic GP (1.41-fold)	
		~20	↑ Plasma glucose (1.14-fold) ↑ Hepatic PEPCK activity (1.21-fold) ↑ Hepatic GP (1.32-fold) No effect at any dose level: Body weight.	
Sprague-Dawley rat pups received diazinon (DZN) or parathion (PRT) by subcutaneous injection. Pups received DZN at 0, 0.5 or 2.0 mg/kg-d, or PRT at 0, 0.1 or 0.2 mg/kg-d on PND1 – PND4.Animals were assessed at PND30, 60, and 100 (body weight was analyzed by MANOVA that incorporated all ages and both sexes) Also presented in study, but not summarized here: Effects on hepatic and cardiac cell signaling mediated through the adenylyl cyclase (AC) cascade: AC activity, responses of β-adrenergic receptors, glucagon receptors, or G-proteins.	6/group	0	Control (DMSO)	(Adigun *et al.* 2010c)
		0.5 mg/kg-d diazinon	↓ Body weight (95% of control) ↓Heart weight (91-92% of control)	
		2.0	↓ Body weight (94% of control) ↓Heart weight (91-92% of control)	
		0.1 mg/kg-d parathion	↔ Body weight ↔ Heart weight	
		0.2	↔ Body weight ↔ Heart weight	
Male Wistar rats (8-weeks old) received fenitrothion (FNT) orally at 0, 25, 50 or	6/group	0	Control (olive oil)	(Afshar *et al.* 2008)
		25 mg/kg-d	Increased total cholesterol (TC) (1.17-fold)	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
100 mg/kg-d for 28 days. Also presented in study, but not summarized here: Effects on red blood cell counts, hemoglobin, hematocrit, mean corpuscular hemoglobin.		fenitrothion 50 100	Decreased triglycerides (TG) (60% of control) ↑ Serum glucose (1.08-fold) ↓Serum protein (89% of control) ↑ Total cholesterol (TC) (1.09-fold) ↓triglycerides (TG) (69% of control) ↑ Serum glucose (1.68-fold) ↑ Total cholesterol (TC) (1.46-fold) ↓ triglycerides (TG) (72% of control)	
Adult female rats received malathion as a single intraperitoneal injection at 0 or 200 mg/kg bw and were killed one hour later. Also presented in study, but not summarized here: Effects of combined treatments with malathione + oximes and malathione + atropine.	not reported	0 500 mg/kg malathion	Control (0.9% NaCl) ↑ fasting glucose (2.19-fold) ↓ Cerebral glycogen (74% of control)	(Agarwal and Matin 1981)
White Leghorn chick embryos were exposed to corn oil or malathion at the 5-day incubation stage; histogenesis of the islets of Langerhans was studied for the 11- to 19-day incubation stages. In the malathion group, only the embryos exhibiting micromelia were studied. Also presented in study, but not summarized here: NA	24 4 – 6 per day (20 total)	0 0.1 mL of 2% per day malathion	Control (corn oil) Relative amounts (%) of pancreatic tissue: ↔ on day 11 and day 19 ↑ % Alpha tissue • 2.16-fold on day 13 • 1.68-fold on day 15 ↑ % Beta tissue • 2.85-fold on day 13 • 2.12-fold on day 15 • 1.91-fold on day 17	(Arsenault and Gibson 1974)
White Leghorn chick embryos were exposed to corn oil or malathion at the 5-day incubation stage; blood sugar levels were determined from the 9-day incubation stage until hatching. All malathion embryos exhibited	83 5 – 18/day (83 total)	0 0.1 mL of 2% per day malathion	Control (corn oil) ↓ Blood sugar level • 96% of control on day 9 • 75% of control on day 11 • 75% of control on day 13 • 84% of control on day 15	(Arsenault *et al.* 1975)

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
micromelia. Also presented in study, but not summarized here: NA			• 73% of control on day 17 • 82% of control on day 19 • ↔ at hatching	
Male albino rats received acephate by daily subcutaneous injection at 0 or 250 mg/kg-d for 8 weeks. Animals were fasted for 24 hours and killed; liver was analyzed for glycogen and blood was analyzed for glucose levels. Also presented in study, but not summarized here: Levels of thiamine, pyruvic acid, and lactic acid in liver, brain, heart, kidney and blood.	8 10	0 250 mg/kg-d acephate	Control (vehicle not described) ↓Liver glycogen (60% of control) ↑Blood sugar (1.37-fold) No effect at any dose level: NA	(Deotare and Chakrabarti 1981)
Babcock BV boiler chickens received monocrotophos at 0 or 2 ppm in the feed for 2 months. Blood was collected for hematological analyses. Also presented in study, but not summarized here: Effects of feeding fenvelarate (a synthetic pyrethroid) or endosulfan (a chlorinated hydrocarbon). T-lymphocyte and B-lymphocytes count; DNFB contact sensitivity test; graft vs. host reaction; NBT salt test; weight and histopathological evaluation of lymphoid organs.	30/group	0 ppm 2 ppm for 2 months monocrotophos	Control (diet) ↑Blood glucose (1.29-fold) No effect at any dose level: Final body weight.	(Garg *et al.* 2004)
Male Wistar rats received malathion by	6/group	0	Control (arachis oil)	(Gowda *et al.* 1983)

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
intraperitoneal injection at 0 or 46 mg/kg-d for 15 days. Also presented in study, but not summarized here: Plasma sodium and potassium and eosinophil count; adrenal ascorbic acid and cholesterol.		46 mg/kg-d malathion	↑Liver glycogen levels • 2.96-fold on day 4 • 2.82-fold on day 8 • 2.77-fold on day 15 ↓Adrenal adrenalin level on day 8 (84% of control) ↓Adrenal noradrenalin level on day 8 (59% of control) ↓Adrenal dopamine level on day 4 (60% of control) No effect at any dose level: Blood glucose; plasma corticosterone.	
Adult male Wistar rats received dimethoate by oral gavage at 0 or 21 mg/kg-d for 2 months; one-half of the dimethoate group was allowed a one-month recovery period. Also presented in study, but not summarized here: NA	10	0	Control (saline)	(Hagar *et al.* 2002)
	20	21 mg/kg-d dimethoate for two months	↑ Serum glucose (1.27-fold) ↓ Serum insulin (1.22-fold) Pancreas Histochemistry: • Reduced succinic dehydrogenase activity, with a negative reaction seen in the most severely affected cells. • Increased acid phosphatase enzymatic activity. Pancreas Histopathology: • Patch degenerative changes affecting the pancreatic acini and the islets of Langerhans.	
	20	21 mg/kg-d for two months with a one-month recovery	↑ Serum glucose (71% of control) ↓ Serum insulin (73% of control) Pancreas Histochemistry: • Reduced succinic dehydrogenase activity, with a negative reaction seen in the most severely affected cells. • Increased acid phosphatase enzymatic activity. Pancreas Histopathology: • Patch degenerative changes affecting the pancreatic acini and the islets of Langerhans.	
Female Wistar rats received diazinon as	10/group	0	Control (normal saline)	(Husain and Ansari 1988)

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
a single intraperitoneal injection at 0 or 40 mg/kg bw and were killed two hours later.		40 mg/kg diazinon	↑ Blood fasting glucose (1.95-fold) ↓ Brain glycogen (53% of control) ↑ Glycogen phosphorylase (1.27-fold) ↑ Phosphoglucomutase (1.48-fold) ↔ Glucose-6-phosphatase Effects were prevented or attenuated when animals were pre-treated with adrenergic-blocking drugs (tolazoline or propranolol) or treated with atropine immediately after diazinon treatment, leading the authors to suggest involvement of cholinergic and adrenergic pathways.	
Adult male CFT-Wistar rats – two experiments: 1) Rats received acephate by oral gavage at 0 or 140 mg/kg bw and blood glucose was estimate every 2 hours for 8 hours.	3/group	0	Control (distilled water)	(Joshi and Rajini 2009)
		140 mg/kg acephate	↑ Blood glucose • 1.87-fold at 2 hours • 1.68-fold at 4 hours • 1.42-fold at 6 hours • 1.16-fold at 8 hours	
2) Rats received acephate by oral gavage at 0 or 140 mg/kg bw and were killed 2 or 6 hours later. Also presented in study, but not summarized here: Effects on organ weights and adrenal cholesterol.	6/group	0	Control (distilled water)	
		140, killed 2 hours post-dose	↑ Blood glucose (1.80-fold) ↑ Plasma corticosterone (1.78-fold) ↑ Glucose-6-phosphatase (1.91-fold) ↑ Tyrosine aminotranferase (1.84-fold) ↔ Hepatic glycogen	
		140, killed 6 hours post-dose	↑ Blood glucose (1.40-fold) ↑ Plasma corticosterone (1.44-fold) ↑ Glucose-6-phosphatase (1.25-fold) ↑ Tyrosine aminotranferase (1.70-fold) ↑ Hepatic glycogen (2.62-fold)	
Adult male CFT-Wistar rats received dimethoate by oral gavage at 0, 20 or 40 mg/kg-d for 30 days.	6/group	0	Control (saline)	(Kamath and Rajini 2007)
		20 mg/kg-d dimethoate	Decreased body weight gain (80% of control) ↑ Pancreas weight (1.12-fold) Impaired glucose tolerance: in the OGTT, the final	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
Also presented in study, but not summarized here: Pancreatic: cholinesterase activity, glutathione levels, oxidative stress markers, activity of antioxidant enzymes, and protein content			blood glucose level was ↑ (1.15-fold) ↑ serum lipase (~1.16-fold) and amylase (~3.25-fold) ↓ pancreatic lipase (~82% of control) and amylase (~37% of control)	
		40	↓ Body weight gain (43% of control) ↑ Pancreas weight (1.32-fold) Impaired glucose tolerance: in the OGTT, the final blood glucose level was ↑ (1.52-fold) ↑ serum lipase (~1.33-fold) and amylase (~4.15-fold) ↓ pancreatic lipase (~92% of control) and amylase (~92% of control)	
White Leghorn chick embryos were exposed to corn oil or malathion at the 5-day incubation stage; histogenesis of the islets of Langerhans was studied during the 11- to 19-day incubation stages.	188	0	Control (corn oil)	(Laley and Gibson 1977)
	17 – 34/day	0.1 mL of 2% per day malathion	↓ Blood sugar level • 77% of control on day 11 • 85% of control on day 15 • 84% of control on day 17 • 84% of control on day 19 Relative amounts (%) of pancreatic tissue: ↑ % Alpha tissue • 1.45-fold on day 15 ↑ % Beta tissue • 1.65-fold on day 15 • 1.34-fold on day 17 The degree of hypoglycemia correlated with the severity of micromelia (leg-shortening) in the chicks.	
Adult male Wistar rats received malathion as a single oral dose at 0 or 400 mg/kg. Animals were killed at 2, 6, 12 or 24 hours after dosing. Also presented in study, but not	12	0	Control (corn oil)	(Lasram *et al.* 2009)
	12/time point (48 total)	400 mg/kg malathion	↑ Plasma fasting glucose at 2-hr (2.32-fold) Hepatic glycogen: • ↓ at 2 hr (46% of control) • ↑ at 6 hr (1.27-fold) • ↑ at 12 hr (1.87-fold)	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
summarized here: Effects of malathion on erythrocyte AChE activity, BChE activity, and plasma protein concentrations (malathion had the predicted effect of decreasing AChE and BChE activities).			• ↑ at 24 hr (1.93-fold)	
Pregnant Long-Evans rats received chlorpyrifos by oral gavage at 0 or 2.5 mg/kg-d from GD7 – PND21. Two males and 2 females from each litter were followed through to young adulthood. On PND95 – PND101, brain and serum were collected; BMIs were determined and serum leptin was quantified. Also presented in study, but not summarized here: Results from dose-response study conducted to confirm F1 male body weight effects; brain RNA assay.	9 – 10 F1 rats/group	0	Control (corn oil)	(Lassiter and Brimijoin 2008)
		2.5 mg/kg-d chlorpyrifos	↑ Male body weights beginning PND51 (~1.07-fold), through PND 72 (1.11-fold) and continuing through termination (1.09-fold) ↑Body volume for males at termination (1.12-fold) ↓ Specific gravity for males at termination (99% of control) ↔Serum leptin (absolute levels). However, chlorpyrifos exposure weakened the weight–leptin correlation in males (r=0.93 for control males vs. r=0.66 for treated males); while in females, it eliminated the statistical significance of the relationship (r=0.87 for control females vs. r=0.44 for treated females).was lepting taken in fasted or unfasted animals? No effect at any dose level: Maternal weight and clinical observations; litter size, F1 neonatal body weight and growth curve prior to weaning; F1 female body metrics; F1 male length and BMI.	
Neonatal Sprague-Dawley rat pups received parathion by subcutaneous injection at 0, 0.1 or 0.2 mg/kg-d on PND1 – PND4. At 15 weeks of age, half the rats were switched to a high-fat diet for 7 weeks. Also presented in study, but not	6 – 12 rats/sex/ treatment	0 (standard diet)	Control (DSMO)	(Lassiter *et al.* 2010)
		0.1 mg/kg-d parathion (standard diet)	↑ male body weight (~1.02 to 1.03-fold) ↓ female body weight (~96% of control) ↑ male fasted serum leptin ↑ adipose TNFα	
		0.2 mg/kg-d (standard diet)	↓ female body weight (~96% of control) ↓ male adiponectin	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
summarized here: TBARS in peripheral tissue and brain.			↑ adipose TNFα	
	6 – 12 rats/sex/ group	0 mg/kg-d (high-fat diet)	Control (DSMO)	
		0.1 mg/kg-d (high-fat diet)	↑ Male fasted serum leptin ↑ Male circulating adiponectin	
		0.2 mg/kg-d (high-fat diet)	↑ Cerebellum weight (~1.1-fold) ↓ Female fasted serum leptin	
Neonatal Sprague-Dawley rat pups received parathion by subcutaneous injection at 0, 0.1 or 0.2 mg/kg-d on PND1 – PND4. At 15 weeks of age, half the rats were switched to a high-fat diet for 7 weeks. Also presented in study, but not summarized here: Lipid homeostasis.	12 rats/sex/ group	0 (standard diet)	Control (DSMO)	(Lassiter *et al.* 2008)
		0.1 mg/kg-d parathion (standard diet)	↑ Male body weight (~1.02-fold) ↑ Female body weight through PND80 (~1.03-fold) ↓ Female body weight after PND84 (~95% of control) ↓ % Female HbA1c	
		0.2 mg/kg-d (standard diet)	↔ Male body weight ↓ Female body weight (~94% control) ↑ glucose levels at 22 weeks ↓ % HbA1c	
	12 rats/sex/ treatment	0 (high-fat diet)	Control (DSMO)	
		0.1 mg/kg-d (high-fat diet)	↔ Male body weight ↑ Female body weight ↓ % Female HbA1c	
		0.2 mg/kg-d (high-fat diet)	↔ Male body weight ↓ Female body weight ↓ % Female HbA1c Not affected at any dose level in either sex or on any diet: Insulin levels at 22 weeks.	
Adult male albino rats received malathion as a single intraperitoneal injection at 0 or 500 mg/kg and were killed 1 hour later. Also presented in study, but not	6/group	0	Control (normal saline)	(Matin and Siddiqui 1982)
		500 mg/kg malathion	↑ Blood fasting glucose (2.27-fold) ↓Brain glycogen: • Cerebral cortex (82% of control) • Corpus striatum (72% of control)	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
summarized here: Effects of combined treatments with malathion + DAM, malathion + atropine, or malathion + reserpine.			• Cerebellum (81% of control) • Medulla (77% of control)	
Adult female albino rats received malathion as a single intraperitoneal injection at 0 or 500 mg/kg and were killed 2 hours later. Also presented in study, but not summarized here: Effects of malathion on brain cholinesterase activity.	8/group	0	Control (normal saline)	(Matin and Husain 1987)
		500 malathion	↑ Blood fasting glucose (2.12-fold) ↑ Blood lactate (1.79-fold) ↓ Brain glycogen (61% of control) ↑ Cerebral glycogen phosphorylate (1.34-fold) ↑ Cerebral phosphoglucomutase (1.58-fold) ↑Hexokinase in brain (1.38-fold) Not affected at any dose level: Blood pyruvate, cerebral glucose-6-phosphatase.	
Adult female albino rats received diazinon as a single intraperitoneal injection at 0 or 40 mg/kg bw and were killed 2 hours later. Also presented in study, but not summarized here: Effects on brain cholinesterase activity	8/group	0	Control (normal saline)	(Matin *et al.* 1990a)
		40 mg/kg diazinon	↑ Blood glucose level (2.06-fold) ↓ Glycogen in brain (67% of control) and liver (64% of control) ↑ Glycogen phosphorylase in brain (1.37-fold) and liver (1.27-fold) ↑ Phosphoglucomutase in brain (1.48-fold) and liver (1.31-fold) ↑Hexokinase in brain (1.26-fold) ↑ Lactate dehydrogenase in brain (1.16-fold) Not affected at any dose level: Glucose-6-phosphatase and Glucose-6-phosphate dehydrogenase in brain and liver. The effects were abolished in the adrenalectomized group.	
Adult female Wistar rats received diazinon as a single intraperitoneal injection at 0, 10, 20 or 40 mg/kg bw	8/group	0	Control (normal saline)	(Matin *et al.* 1989)
		10 mg/kg diadzinon	No significant effect	
		20	↑ Blood glucose (1.49-fold)	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
and were killed 2 hours later. Also presented in study, but not summarized here: Effects on brain cholinesterase activity			↓ Glycogen in brain (85% of control) and liver (84% of control)	
		40	↑ Blood glucose (1.99-fold) ↓ Glycogen in brain (64% of control) and liver (70% of control) ↑ Glycogen phosphorylase in brain (1.37-fold) and liver (1.27-fold) ↑ Phosphoglucomutase in brain (1.48-fold) and liver (1.31-fold) ↑Hexokinase in brain (1.26-fold) ↑ Lactate dehydrogenase in brain (1.17-fold) Not affected at any dose level: Glucose-6-phosphatase and Glucose-6-phosphate dehydrogenase in brain and liver. The effects were abolished in the adrenalectomized group.	
Adult female albino rats received diazinon as a single intraperitoneal injection at 0, 10, 20 or 40 mg/kg bw and were killed 2 hours later. Also presented in study, but not summarized here: Effects on brain cholinesterase activity; brain and hepatic gluconeogenic enzyme activities; results from the adrenalectomized group.	8/group	0	Control (normal saline)	(Matin *et al.* 1990b)
		10 mg/kg bw diazinon	No significant effect	
		20	↑ Blood glucose (1.46-fold) ↓ Glycogen in brain (83% of control) and liver (82% of control) ↑ Glycogen phosphorylase in liver (1.13-fold) ↑ Phosphoglucomutase in brain (1.25-fold) ↑Hexokines in brain (1.16-fold) ↑ Lactate dehydrogenase in brain (1.06-fold)	
		40	↑ Blood glucose (2.00-fold) ↓ Glycogen in brain (70% of control) and liver (64% of control) ↑ Glycogen phosphorylase in brain (1.38-fold) and liver (1.26-fold) ↑ Phosphoglucomutase in brain (1.49-fold)	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
			↑Hexokines in brain (1.29-fold) ↑ Lactate dehydrogenase in brain (1.12-fold) Not affected at any dose level: Glucose-6-phosphatase and Glucose-6-phosphate dehydrogenase in brain and liver. The effects were abolished in the adrenalectomized group.	
Female Long-Evans rats received chlorphyrofos by subcutaneous injection at 0 or 5 mg/kg-d for 4 months. Also presented in study, but not summarized here: NA	10/group	0	Control (placebo)	(Meggs and Brewer 2007)
		5 mg/kg-d chlorpyrifos	↑ Body weight • 2 months (1.05-fold) • 3 months (1.09-fold) • 4 months (1.10-fold) ↑ weight of peri-nephric fat pad (2.5-fold) Not affected at any dose level: Weight of heart, liver, or gastrocnemius muscle; adipocyte differentiation in tissue culture.	
Adult male Wistar rats received malathion in the diet at 0, 100, 200 or 400 ppm for 4 weeks. The rats were killed, blood was collected and analyzed for glucose and insulin levels; and pancreatic islets were isolated and assayed for glutamate dehydrogenase (GDH) and glucokinase (GK) activity. Also presented in study, but not summarized here: NA	6/group	0 ppm	Control diet with almond oil	(Panahi *et al.* 2006)
		100 ppm malathion	↑Blood glucose (1.16-fold), ↑Islet GDH activity (1.28-fold)	
		200	↑Blood glucose (1.18-fold) ↑Blood insulin (2.38-fold) ↑Islet GDH activity (1.60-fold) ↑Islet GK activity (1.31-fold)	
		400	↑Blood glucose (1.18-fold) ↑Blood insulin (2.46-fold) ↑Islet GDH activity (2.35-fold) ↑Islet GK activity (1.66-fold) No effect at any dose level: Body weight	
Adult male Wistar rats received malathion as a single intraperitoneal	6	0	Control (saline)	
		3 mg/kg malathion	↑Blood glucose (1.18-fold)	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
injection at 3, 15, or 75 mg/kg bw. One hour after dosing the rats were killed, blood was collected and analyzed for glucose and insulin levels; and pancreatic islets were isolated and assayed for glutamate dehydrogenase (GDH) and glucokinase (GK) activity. Also presented in study, but not summarized here: NA			↑Islet GDH activity (1.62-fold)	
		15	↑Blood glucose (1.45-fold) ↑Blood insulin (1.21-fold) ↑Islet GDH activity (1.79-fold) ↑Islet GK activity (1.22-fold)	
		75	↑Blood glucose (1.59-fold) ↑Blood insulin (1.28-fold) ↑Islet GDH activity (2.41-fold) ↑Islet GK activity (1.57-fold) No effect at any dose level: NA	
Male Wistar rats received malathion in the diet at 0, 100, 200 or 400 ppm for 4 weeks. After an 18-hour fast, the rats were killed and skeletal muscle and blood were collected. Plasma was analyzed for glucose and insulin levels; muscle was analyzed for phosphofructokinase (PFK), glycogen phosphorylase (GP) and hexokinase (HK) activity. Also presented in study, but not summarized here: NA	8/group	0 ppm	Control diet with almond oil	(Pournourmohammadi *et al.* 2005)
		100 ppm malathion	↑Muscle PFK activity (1.40-fold)	
		200	↑Plasma glucose (1.44-fold) ↑Plasma insulin (2.36-fold) ↑Muscle PFK activity (1.54-fold)	
		400	↑Plasma glucose (1.61-fold) ↑Plasma insulin (2.43-fold) ↑Muscle PFK activity (1.83-fold) ↑Muscle GP activity (1.92-fold) No effect at any dose level: Muscle HK activity.	
Female rats received malathion as a single subcutaneous injection at 0, 2 or 2.5 mg/kg bw. Also presented in study, but not summarized here: Mitigating effects of adrenalectomy, adrenalectomy and triamcinolone, pentapyrrolidonium, reserpine, atropine, N-methyl-atropine; effects on serum cholinesterase.	5	0	Control (vehicle – xylene)	(Ramu and Drexler 1973)
	7	2 mg/kg malathion	Increased* peak blood fasting glucose (2.34-fold)	
	7	2.5	Increased* peak blood fasting glucose (2.16-fold) * No statistical analysis performed	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
Male albino rats received dimethoate by daily intraperitoneal injection at 0 or 150 mg/kg bw on alternate days for 15 (10 dimethoate-treated rats) or 30 days (remaining rats). Rats were fasted overnight; blood was collected and the serum was analyzed for levels of glucose and cholesterol, and the activities of glutamic-oxalacetic (SGOT) and glutamic-pyruvic transaminases (SGPT). Also presented in study, but not summarized here: Hematology parameters; serum levels of amylase, urea and total bilirubin; activities of alkaline and acid phosphatases and cholinesterase.	10	0	Control (saline)	(Reena *et al.* 1989)
	20 (10/ time point)	150 mg/kg dimethoate on alternate days	↑Serum glucose after 30 days (1.26-fold) ↑Serum cholesterol after 30 days (1.17-fold) ↑SGOT after 30 days after 30 days (1.36-fold) ↑SGPT after 15 days (2.21-fold) and after 30 days (3.18-fold) No effect at any dose level: NA	
Adult male Wistar rats received malathion by gavage at 0 or 100 mg/kg-d for 32 days. Also presented in study, but not summarized here: Effects on plasma acetylcholinesterase activity, hematology, hepatic proteins and hepatic lipids.	12/group	0	Control (corn oil)	(Rezg *et al.* 2007)
		100 mg/kg-d malathion	↓ Musculature glycogen rate (70% of control) ↑ Hepatic glycogen rate (1.50-fold) Not affected at any dose level: Blood glucose.	
Male Wistar rats received a single intraperitoneal injection of malathion at 0 or 650 mg/kg bw. Blood glucose was measured for 24 hours. Also presented in study, but not summarized here: Glucose utilization by swine IB-RS-2 cells.	40 (5/time point)	0	Control (DMSO)	(Rodrigues La *et al.* 1986)
		650 mg/kg malathion	Compared to control levels, increased* blood glucose was observed in the first hour of treatment, reached a peak after 2 hr (2.2-fold), decreased after 4 hr (~1.8-fold) and 8 hours (~1.2-fold) - returning to normal by 24 hours. **statistical analysis not performed*	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
Male and female Sprague Dawley rat pups received diazinon by subcutaneous injection at 0, 0.5 or 2.0 mg/kg-d on PND1 – PND4. On PND105, one half of the rats were placed on a high-fat diet for 5 weeks and then returned to a normal diet for 2 more weeks. Also presented in study, but not summarized here: Effects on emotional reactivity as adults.	10-12/sex	0 diazinon	Control (DMSO)	(Roegge *et al.* 2008)
		0.5 mg/kg-d diazinon (normal diet)	No significant effect	
		0.5 mg/kg-d (high-fat diet)	↑ Body weight gain after switch to high-fat diet (~1.04 – ~1.18-fold for males; ~1.05 – ~1.19-fold for females)	
		2.0 mg/kg-d (normal diet)	No significant effect	
		2.0 mg/kg-d (high-fat diet)	No significant effect	
Male Wistar rats received dichlorvos [route not stated] at 0 or 20 mg/kg bw. After 1 or 3 days of treatment, rats were killed and liver was collected and analyzed for glucokinase activity and glucokinase mRNA levels. Pancreatic islets were isolated and analyzed for glucokinase activity and glucokinase mRNA and insulin mRNA levels. Also presented in study, but not summarized here: NA	3-4 /assay	0	Control (corn oil)	(Romero-Navarro *et al.* 2006)
		20 mg/kg dichlorvos	↓Hepatic glucokinase activity after 1 day (49% of control) and after 3 days (51% of control) ↑Hepatic glucokinase mRNA levels after 1 day (1.86-fold) and after 3 days (~2.2-fold). No effect at any dose level: Pancreatic glucokinase activity, glucokinase mRNA levels, or insulin mRNA levels.	
Adult male mice were exposed to azynphos methyl (AZP) or malathion (MLT) by dipping their tails in 0%, 0.1%, 1% or 10% solutions for 10 seconds on seven consecutive days. Also presented in study, but not summarized here: NA	6	0%	Control (water)	(Sadeghi-Hashjin *et al.* 2008)
		0.1% AZP	No significant effect	
		1% AZP	No significant effect	
		10% AZP	(all mice died within 24 hours)	
		0.1% MLT	No significant effect	
		1% MLT	↓ Postprandial blood glucose on Day 1 (67% of control)	
		10% MLT	No significant effect Not affected at any dose level: Fasting glucose levels.	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
Time Course Study: Swiss albino mice (4 – 8 weeks old) received diazinon as a single intraperitoneal injection of 150 mg/kg bw. Blood glucose was measured at intervals spanning 22 days.	5/time point	0	Control (2-year historical control average)	(Seifert 2001)
		150 mg/kg diazinon	Increased blood glucose by 3 hours post dose (3.24-fold), and at ~50 hours (~1.6-fold), ~67 hours (1.35-fold), and ~150 hours (~1.25-fold) post dose.	
Dose Response Study: Swiss albino mice (4 – 8 weeks old) received a single intraperitoneal injection of diazon at 0, 20, 75, 100, 150 or 250 mg/kg bw. Blood glucose was measured 1.5 hours after dosing.	5/group	0	Control (triethylene glycol dimethyl ether)	
		20 mg/kg diazinon	No effect	
		75	Increased glucose (~1.3-fold)	
		100	Increased glucose (~1.8-fold)	
	25	150	Increased glucose (~2.1-fold)	
	5	250	Increased glucose (~1.85-fold)	
Effect of diet availability: Swiss albino mice (4 – 8 weeks old) received diazinon as a single intraperitoneal injection of 150 mg/kg bw. Half the mice were maintained on a restricted diet [not described] and the other half were fed *ad libitum*. Blood glucose was measured 1.5 – 2.5 hours after dosing.	5 mice on restricted diets, 5 mice fed *ad libitum*	150 mg/kg diazinon	There was no difference in blood glucose levels between mice on a restricted diet and mice fed *ad libitum* [data not shown].	
Diurnal Response: Swiss albino mice (4 – 8 weeks old) received diazinon as a single ip injection of 150 mg/kg bw at 08:00, 14:00, 20:00, or 01:00 hours. Blood glucose was measured 1.5 hours after dosing.	5/time point	0	Control (triethylene glycol dimethyl ether)	
		150 mg/kg diazinon	Blood glucose was higher in mice treated during the day, than at night: 08:00 – 1.85-fold, 14:00 – 1.9-fold, 20:00 – 1.7-fold, 01:00 – 1.4-fold	
Neonatal Sprague-Dawley rats received chlorpyrifos by subcutaneous injection at 0 or 1 mg/kg-d on PND1 – PND4. Animals assessed at PND 110 and 120 Also presented in study, but not summarized here: NA	8/sex	0	Control (DMSO)	(Slotkin *et al.* 2005)
		1 mg/kg-d diazinon	↑ Plasma insulin in non-fasted males (~1.6-fold) ↑Plasma cholesterol in males (1.35-fold) ↑Plasma triglycerides in males (1.35-fold) Not affected at any dose level: Growth, viability, body weights; plasma nonesterified free fatty acids, glycerol, and glucose concentrations; plasma lipids in females.	

Appendix Tables

(version updated January 3, 2011)

Appendix Table A. Summaries of Organophosphorus Compound Studies in Experimental Animals

Species, strain, and experimental design	Sample size	Dose	Effects	Reference
Male Wistar and GK (mildly diabetic) rats received diazinon as a single intraperitoneal injection at 0 or 6.5 mg/kg bw. 3-hour OGTTs were conducted pretreatment and at 1 and 2 weeks post treatment. Also presented in study, but not summarized here: Effects of diazinon on the activity of hepatic drug-metabolizing enzymes and expression of hepatic cytochrome P450 (CYP) 1A2, CYP3A2 and CYP2D1; plasma cholinesterase activity.	3 – 4	0 (Wistar Rats)	Control (0.9% CMC)	(Ueyama *et al.* 2008)
		6.5 mg/kg diazinon (Wistar Rats)	No significant effect	
		0 (GK Rats)	Control (0.9% CMC)	
		6.5 mg/kg bw diazinon (GK Rats)	↑ Blood glucose at 1 week post-treatment: • 60 minutes - ~1.55-fold over pretreatment level ↑Glucose AUC at 1 week post-treatment (1.27-fold over pretreatment) ↑Blood glucose at 2 weeks post-treatment • 60 minutes - ~1.90-fold over pretreatment level • 120 minutes - ~1.91-fold over pretreatment level • 180 minutes - ~2.00-fold over pretreatment level ↑Glucose AUC at 2 week post-treatment (1.72-fold over pretreatment) Not affected in Wistar or GK rats: pancreatic histopathology; difference in the structure and number of islet immunoreative insulin-positive cells; GLUT4 expression	

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